Protocol Number: P-105-201

Official Title: Phase 2 Multicenter, Randomized, Double-blind, Placebo- Controlled, Multiple Dosing Interval, 2-Period Study of the Safety, Tolerability and Effectiveness of Adoptively Transferred Posoleucel (ALVR105) Multivirus-Specific T Cells in Kidney Transplant Recipients with either High or Low Levels of BK Viremia

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STATISTICAL ANALYSIS PLAN

Protocol Title:	Phase 2 Multicenter, Randomized, Double-blind, Placebo-Controlled, Multiple Dosing Interval, 2-Period Study of the Safety, Tolerability and Effectiveness of Adoptively Transferred Posoleucel (ALVR105) Multivirus-Specific T Cells in Kidney Transplant Recipients with either High or Low Levels of BK Viremia
Protocol Number:	P-105-201
Protocol Version/Date:	V4.0/30 Sep 2021
Investigational Product:	Posoleucel (ALVR105, formerly known as Viralym-M)
Sponsor:	AlloVir 1100 Winter Street Waltham, MA 02451 United States
SAP Version/Date:	Final Version 1.0 / 28-November-2022

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Protocol Title: Phase 2 Multicenter, Randomized, Double-blind, Placebo-Controlled, Multiple Dosing Interval, 2-Period Study of the Safety, Tolerability and Effectiveness of Adoptively Transferred Posoleucel (ALVR105) Multivirus-Specific T Cells in Kidney Transplant Recipients with either High or Low Levels of BK Viremia

Protocol Number: P-105-201

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

Signature **Date**

Prepared by: [redacted]

29 Nov 2022 01:40:16 UTC (Z

REASON: I approve this d cument

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Approved by: [redacted]

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REASON: I have reviewed this docu mer t and have no comments that require addressi

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AdV	Adenovirus
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ALVR105	Posoleucel (formerly Viralym-M)
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BKV	BK Virus
CI	Confidence Interval
CMV	Cytomegalovirus
CRF	Case Report Form
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
ECG	Electrocardiograms
eGFR	estimated Glomerular Filtration Rate
GVHD	Graft vs Host Disease
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHV-6	Human Herpesvirus 6
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IFN	Interferon
IQR	Interquartile Range
ITT	Intent-to-Treat
IV	Intravenous(ly)
JCV	JC Virus
LOCF	Last Observation Carried Forward
MDRD	Modified Dose in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PSL	Posoleucel or ALVR105 (formerly Viralym-M)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal
Viralym-M	Posoleucel or ALVR105
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 Study P-105-201 under Protocol Version 4.0, 30 Sep 2021. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare the safety and tolerability of posoleucel (PSL, ALVR105, formerly Viralym-M) to placebo in kidney transplant recipients.

2.1.2 Secondary Objectives

The key secondary objective is to assess the overall efficacy of PSL to suppress BK viral load compared with placebo.

The other secondary objective is to compare the relative efficacy of different dosing regimens of PSL to suppress BK viral load versus placebo.

2.1.3 Exploratory Objectives

The exploratory objectives include comparisons of the following in recipients of PSL and in patients receiving placebo:

- To assess change in estimated glomerular filtration rate (eGFR) over 24 weeks in recipients of PSL versus placebo
- To identify changes in donor-specific anti-human leukocyte antigen (anti-HLA) antibodies in recipients of PSL versus placebo
- To determine the proportion of patients with resolution of BK viremia at 8 weeks post virus-specific T cell infusion
- To assess kidney allograft survival at 24 weeks
- To assess the incidence of recrudescent or new infections with target viruses (including cytomegalovirus [CMV]), but principally BKV
- To determine whether patients with initially low BK viral load (ie, <10,000 copies/mL) can be prevented from developing viremia ≥10,000 copies/mL that leads to new or increased immunosuppression reduction
- To determine whether patients with initially low BK viral load (ie, <10,000 copies/mL) in the investigational arm(s) develop lower viral loads than the placebo arm

2.2 Study Design

2.2.1 Overview

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, multiple dosing interval, 2-period study of the safety, tolerability and efficacy of adoptively transferred PSL virus-specific T cells in kidney transplant recipients with BK viremia.

This study is comprised of 2 periods. Period 1 includes a 2-week window for screening assessments followed by a 12-week treatment period for eligible patients. Period 2 (consists of a 12-week) follow-up. Overall, the total duration of patient participation in the study is approximately 26 weeks (2 weeks for screening, 12 weeks of treatment, and 12 weeks of follow-up).

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized to receive PSL or placebo infusions. Patients will be stratifie [redacted] atients will be monitored following randomization for safety, BK viral load, renal function, and immune function, including modification of immunosuppression reduction. Patients will be monitored following randomization for safety, BK viral load, renal function, and immune function, including modification of immunosuppression reduction.

Patients will receive infusions of either PSL or placebo for 12 weeks. [redacted] All infusions will be administered IV (via peripheral or central line) over approximately [redacted] as a slow push. Patients will receive the same dose for all infusions.

The study will consist of 3 treatment arms. To maintain the blind, all patients will receive an infusion (either PSL or placebo) weekly for the first 3 weeks of the dosing period, followed by every other week dosing for the remaining 9 weeks. The treatment arms and associated infusions are as follows:

[redacted]

Administrative interim analyses are planned for the study as described in Section 3.7. The Sponsor's study team and Investigators will remain blinded to individual patient data during and after the administrative interim analyses.

After the first 3 doses, patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart will discontinue PSL infusions. If a patient's viral load becomes undetectable, such a patient may be followed every 14 days for study evaluations as per the Schedule of Activities. Patients will not be permitted to receive a subsequent infusion of PSL if they develop new onset graft vs host disease (GVHD) ≥Stage 1 or cytokine release syndrome (CRS) > Grade 2 at the proposed time for infusion of any subsequent dose.

A summary of study design is shown in Figure 1.

2.2.2 Study Drug

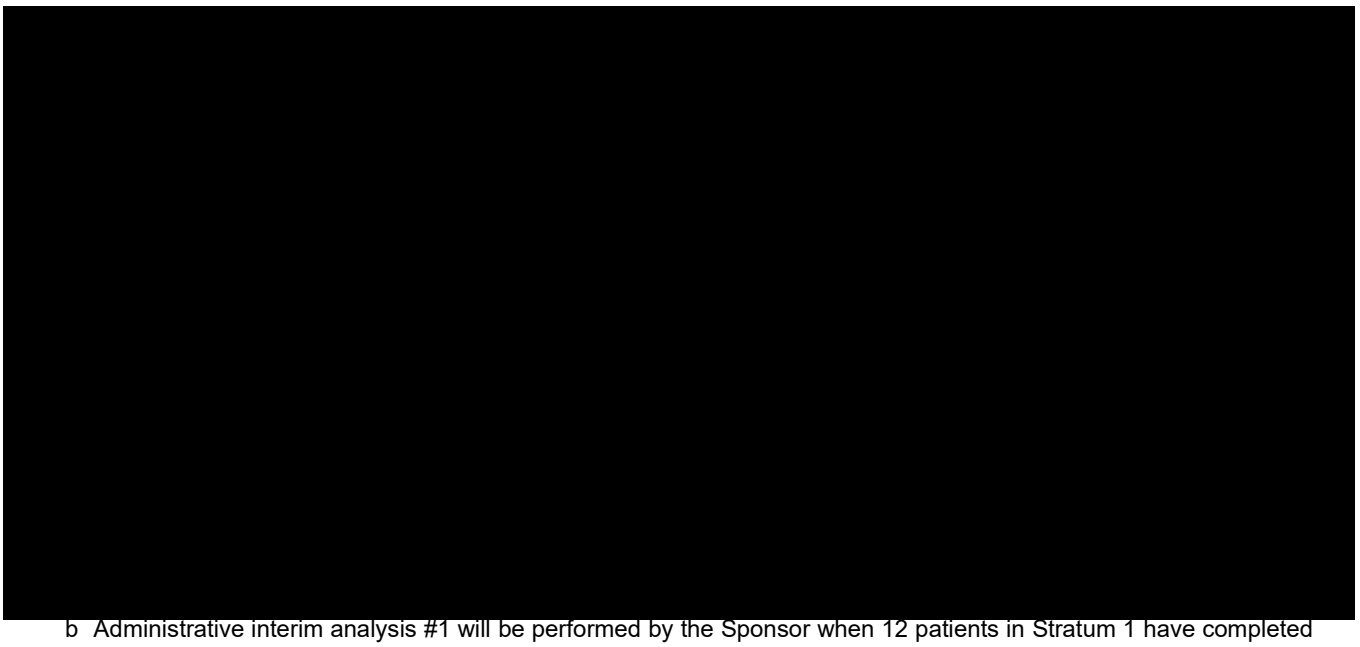
PSL is a third-party, donor-derived, "off-the-shelf," virus-specific T cell product with specificity for BKV, AdV, CMV, EBV, and HHV-6 (with additional cross-reactive specificity for JCV) that is cryopreserved and ready for immediate use. Cryopreservation media (without cells) will serve as the placebo and will be identical in volume and appearance when administered.

2.2.3 Sample Size Determination

No formal sample size determination was made for this study, whose primary endpoint is safety and tolerability. Approximately 60 patients will be randomized at approximately 38 clinical sites. Patients (n=20 in each arm) will be randomized to receive PSL (administered at a dose interval of every 14 or 28 days after 3 initial weekly doses) or placebo.

Patients will be stratified [redacted] A minimum of 6 patients must be enrolled in each stratum, but the remaining patients can be enrolled in either stratum.

Figure 1. Study Flow Chart



b Administrative interim analysis #1 will be performed by the Sponsor when 12 patients in Stratum 1 have completed 8 weeks in the study. Administrative interim analysis #2 will be performed when 30 patients have completed 8 weeks in the study. Interim analyses may be omitted or added at the discretion of the Sponsor to allow for long term planning, and to assess ending the study or either arm early.

Abbreviations: BKV=BK virus; Q=every; S/P=status post

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint is safety and tolerability assessed by treatment-emergent adverse events (TEAEs) and changes in vital signs, physical examinations, clinical laboratory assessments, and ECGs in kidney transplant recipients.

2.3.2 Secondary Efficacy Endpoints

The key secondary endpoint is change in BK viremia in patients receiving PSL compared to patients receiving placebo.

The other secondary efficacy endpoint is change in BK viremia in patients receiving different dosing regimens of PSL or placebo.

The comparison will be based on quantitation of plasma BK viral load performed at the central laboratory. Viral load will be quantitated using polymerase chain reaction assays.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include comparison between results in patients receiving PSL versus placebo for the following:

- Change in eGFR by Modified Dose in Renal Disease (MDRD) formula.
- Changes from baseline in levels of donor-specific anti-HLA antibodies.

- Proportion of patients with resolution of BK viremia at 8 weeks post virus-specific T cell infusion.
- Proportion of patients with eGFR >20 mL/min at 24 weeks.
- Incidence of new target viral infections or recrudescent infections (i.e., BKV, CMV, EBV, AdV, JCV, and/or HHV-6) as defined by onset of viremia and/or the presence of associated symptoms relative to baseline.
- Length of BKV remission (i.e., time from clearance of BK viremia to reappearance of BK viremia (plasma viral load >156 copies/mL × 2 measures that are at least 2 weeks apart) or end of study).
- Number of patients with screening BK viremia < 10,000 copies/mL who develop BK viremia ≥10,000 copies/mL (sustained or non-sustained) or who experience a medically significant event that leads to changes in immunosuppression reduction.
- The absolute viral load in patients in the investigational arms versus that in patients in the placebo arm with screening BK viremia <10,000 copies/mL.

2.3.4 Other Endpoints

The other endpoints include the following:

- Frequency and severity (adjudicated Banff classification) of biopsy-proven acute allograft rejection in recipients of PSL versus placebo.
- Number of patients in the investigational arms with polyomavirus haufen in the urine as compared to the placebo arm.
- Quantification of IFN-ɣ (+) T cells specific for BK virus in patients in the investigational arms as compared to the placebo arm.
- Levels of (virus-specific T cell) donor T cell deoxyribonucleic acid (DNA) as compared to patient T cell DNA in peripheral blood.
- Time to resolution of non-BK target viral infections (i.e., associated signs, symptoms, and presence/absence of HHV-6, EBV, JCV, and/or AdV viremia) present at the time of randomization.
- Use of immunosuppressive agents, including specific immunosuppressive agents used, doses, and any changes in dose.
- Number of hospitalizations/re-hospitalizations for any reason and number of days.
- Incidence and duration of use of any other antiviral therapies during the study.
- Time to death (from any cause) from the time of randomization.
- Number of patients with kidney injury requiring hemodialysis.
- Rate of decline of BK viremia in recipients of PSL using different dosing intervals versus that in patients receiving placebo.

- Assessment of renal function (eGFR estimated by the creatinine-cystatin C method reported by central lab).

The biomarker data, including IFN-ɣ (+) T cells specific for BK virus, polyomavirus haufen in the urine, and T cell receptor sequencing data will not be analyzed in this SAP but reported separately.

2.3.5 Safety Endpoints

Safety endpoints include treatment-emergent adverse events (TEAEs), change in vital signs, physical examination findings, clinical laboratory evaluations (clinical chemistry, hematology, urinalysis, pregnancy testing and other screening tests), and 12-lead Electrocardiograms (ECGs).

The adverse events of special interest (AESI) include infusion-related AEs, GVHD, and CRS. Grading criteria for GVHD and CRS can be found in Appendix 5 (Protocol Section 10.5) and Appendix 6 (Protocol Section 10.6), respectively. These AESIs will be reviewed by the DSMB as per the DSMB Charter.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Study Day

Analysis day will be calculated from the date of first dose of study drug, as analysis day = actual visit date – first dose date + 1. 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.

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. If a subject's day 1 samples are taken after the initial infusion, the samples taken prior to cycle 1 day 1, such as screening samples, may be used as the baseline values.

3.1.4 Summary Statistics

Summary statistics will be presented by treatment group and stratum. Unless otherwise stated, continuous variables will be summarized using the number of non-missing observations,

arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized using the frequency count and the percentage of patients in each category as descriptive statistics.

3.1.5 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.

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.

Viral load values below the limit of quantification will be imputed as the limit of quantification minus 0.1 unit (for CMV) or minus 1 unit (for other viruses).

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all randomized patients regardless of whether the patient actually receives PSL or placebo. Patients will be analyzed according to the randomized study treatment.

3.2.2 Modified Intent-to-Treat (mITT) Population

The modified Intent-to-Treat (mITT) Population will include all randomized patients who have the disease under study and who receive any amount of PSL or placebo. Patients will be analyzed according to the randomized study treatment. Analyses using mITT may be set aside if it is determined that the ITT population and the mITT Population are identical.

3.2.3 Safety Population

The Safety Population will include all patients who receive any amount of PSL or placebo. All safety analyses will be based on the Safety Population. Patients will be analyzed according to the treatment actually received.

3.3 Patient Data and Study Conduct

Unless otherwise noted, safety listings and tables will be presented for Safety Population based on the actual treatment. Efficacy listings will be presented for ITT Population based on the randomized study treatment. Efficacy summary tables and statistical analysis will be presented for ITT population as indicated in Table 1.

3.3.1 Patient Disposition

All patients who provided informed consent will be included in a summary of patient disposition. The numbers and percentages of patients who were screened, screen failure along with the reasons of screen failure, randomized, completed study drug, discontinued study drug early, completed the study and discontinued the study early will be summarized along with the reasons for early discontinuation of study and study drug.

The numbers and percentages of patients in each analysis population with reasons for exclusion will also be summarized.

By patient listing will also be provided for patient disposition, screen failures, patients who were randomized and reason for exclusion from analysis population.

3.3.2 Protocol Deviations

The numbers and percentages of patients with protocol deviations by deviation category will be summarized for ITT population.

All protocol deviations will be listed by patient.

3.3.3 Demographic and Baseline Characteristics

Demographic (age, sex, race, and ethnicity) and baseline characteristics (height, weight and body mass index at baseline) will be summarized with descriptive statistics or counts and percentages of patients as appropriate. The summaries will be provided for ITT and safety populations, unless these are identical (all randomized patients are treated), in which case only the ITT version will be provided.

In addition, these following categories will be presented in listings:

- Childbearing potential
- Number of matched HLA alleles and class (I, II and I&II) between the cell line and study patient, and between the cell line and kidney transplant donor
- Any other relevant disease characteristics, such as GFR, BK viral load, and immunosuppressive medications at Baseline

All the HLA analyses will be based on CytoMatch data, not the EDC HLA data.

3.3.4 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.

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

In addition, underlying disease for kidney transplantation will be listed.

3.3.5 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 safety population.

A by-patient listing will be provided for prior and concomitant medications.

3.3.6 Immunosuppression Therapy

Immunosuppression therapy will be presented similarly as concomitant medication.

An immunotherapy dose reduction will be defined as a reduction of 50% or greater of the current dose when compared to the dose at Baseline.

3.3.7 Study Drug Exposure and Compliance

Study drug duration, number of doses, and total dosing will be summarized based on the Safety Population.

The length of exposure to study drug (PSL or Placebo) will be calculated as the number of days from the first dose of double-blind study to 14 days after the last dose of double-blind study drug, regardless if the patient missed one or more doses of study drug. Length of exposure will be summarized by treatment group using descriptive statistics for the safety population.

A by-patient listing will be provided for study drug exposure.

Overall compliance will be calculated as:

*(Sum of total volume administered)/ (total volume of planned)*100*

The number and percentage of patients will be summarized by treatment group for the Safety Population for the following categories 0- <75%; >= 75%.

For patients who discontinue treatment per protocol for resolution of viremia, the total planned volumes will be calculated up to the last dosing date.

The study drug administration and compliance data, including reasons for poor compliance if noted in the CRF, will be listed for each patient.

3.4 Efficacy Analyses

This section describes the analysis to be conducted for the key secondary, other secondary and exploratory efficacy endpoint along with other endpoints. The efficacy analysis will be performed on the ITT population unless otherwise stated. Analyses using mITT may be set aside if it is determined that the ITT population and the mITT Population are identical. Unless otherwise specified, the results of efficacy analysis and all the summary tables will be presented by stratum and treatment group.

3.4.1 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is change from Baseline in BK viremia in both copies/mL and log10 copies/mL in patients receiving PSL (pooled PSL) compared to patients receiving

placebo, based on quantitation of viremia performed at the central laboratory. The other secondary efficacy endpoint is change in BK viremia in patients receiving different dosing regimens of PSL compared to patients receiving placebo in copies/mL and log10 copies/mL. Change in BK viremia will be assessed by BK viral load assessments.

Observed, change from baseline and percent change from baseline values for BK viral load will be summarized by visit and treatment using descriptive statistics. Percentage change of BK viral load from baseline at each post baseline visit will be presented to determine the rate of decline of BK viremia. Listing will be provided for BK viral load.

AUC for BK viral load (in log 10 copies/ml) adjusted by time duration (area divided by days) will be summarized at each post-baseline timepoint by treatment arm using descriptive statistics. Listings will be provided for AUC of BK viral load.

Two different plots of BK viral load and change from Baseline (both copies/mL and log scale) will be presented for both mean+/- SD and median & IQR by visit for (Arm 1, Arm 2 and Arm 3) and (Arm 1+2 and Arm 3).

Two sets of figures will be produced for mean+/- SD for percent change from baseline (day 1) for BK-viral load for (Arm 1, Arm 2 and Arm 3) and (Arm 1+2 and Arm 3).

Two sets of figures will be produced for both mean+/- SD and median & IQR for AUC for (Arm 1, Arm 2 and Arm 3) and (Arm 1+2 and Arm 3).

3.4.2 Exploratory Efficacy Endpoints

Observed results, change from Baseline, and percent change from baseline for eGFR estimated by MDRD and creatinine will be summarized by visit using descriptive statistics.

Donor specific anti-HLA antibodies (DSA) (yes/no) will be summarized by visit using descriptive statistics.

Resolution of viremia will be generally defined as achieving a post-baseline viral load measure below the lower limit of quantification (<LLOQ) for that viral assay. The number of patients with resolution for each virus (BKV, CMV, EBV, AdV, JCV, and/or HHV-6) will be summarized by visit and at any visits. In addition, the proportion of patients reaching at least 1 log10 reduction or <LLOQ in BK viral load post infusion will be summarized by visit and at any visits.

LLOQ values for the viruses of interest are:

BKV Viral Load (Copy/mL): LLOQ = 156

Non-BK Target Viruses:

ADV Viral Load (Copy/mL): LLOQ = 32

CMV Viral Load (Copy/mL): LLOQ = 65.6

EBV Viral Load (Copy/mL): LLOQ = 37

HHV-6 Human Herpesvirus 6 (Copy/mL): LLOQ = 110

JCV JC Virus (IU/mL): LLOQ = 76

Time-to-event endpoints will be summarized using the Kaplan-Meier method. 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.

Time to resolution of BK viremia will be calculated as starting at randomization for patients with detectable virus and ending at the first undetectable viral load (i.e., <LLOQ). Patients who discontinued from the study early or deceased before they are observed to have achieved resolution will be censored at the last assessment date for this endpoint.

For patients who reach the resolution of BK viremia, time to reappearance of BK viremia (duration of viral remission) will be calculated as starting at the first assessment with undetectable viral load and ending at the first detectable viral load (confirmed with 2 consecutive measures at least 8 days apart, or end of study if only one measure is available). Patients not demonstrating the reappearance of viremia would be censored on the date of the latest assessment for this endpoint. Patients who discontinued from the study early or deceased before they are observed to have will be censored at the last assessment date for this endpoint.

Time to resolution of non-BK target viral infections (i.e., associated signs, symptoms, and presence/absence of CMV, HHV-6, EBV, JCV, and/or AdV viremia) will not be performed due to limited number of events for each virus. The time to death will not be performed but the deaths will be summarized and listed.

To evaluate the impact of missing data at some timepoints, a sensitivity analysis will also be performed on BK viremia using last observation carried forward imputation.

In addition, the number and percentage for patients will be presented for following endpoints by visit unless otherwise stated.

- Patients with eGFR >20 mL/min/1.73m^2 at 24 weeks
- Patients with incidence of new target viral infections or recrudescent infections (i.e., BKV, CMV, EBV, AdV, JCV, and/or HHV-6) as defined by onset of viremia.

  The associated symptoms are not collected so will not be considered.
- Patients with screening BK viremia <10,000 copies/mL who develop BK viremia ≥10,000 copies/mL (sustained or non-sustained) or who experience reduction of immunosuppression which is defined as a reduction of 50% or greater of the current dose when compared to the dose at Baseline for the following medications: tacrolimus, Prograf, Envarsus, cyclosporine, Neoral Sandimmune, everolimus, sirolimus, Rapamune, rapamycin, mycophenolate mofetil, mycophenolate sodium, mycophenolic acid, Cell Cept, Myfortic, azathioprine).
  - The following drugs would not be considered for immunosuppression reduction: Prednisone, methylprednisolone, glucocorticoids, Leflunomide, Arava, Gammagard or IVIG.

Two sets of figures will be produced for mean+/- SD for change from baseline for eGFR for (Arm 1, Arm 2 and Arm 3) and (Arm 1+2 and Arm 3).

Two sets of figures will be produced for mean+/- SD for change from baseline for Creatinine for (Arm 1, Arm 2 and Arm 3) and (Arm 1+2 and Arm 3).

Listings will be provided for viral loads, eGFR, creatinine, HLA related information and donor specific anti-HLA antibodies.

3.4.3 Other Endpoints

Observed results, change from baseline, and percent change from baseline for eGFR (estimated by the creatinine-cystatin C method) will be summarized by visit using descriptive statistics. The number of days of hospitalizations and re-hospitalizations for any reason will be summarized.

Number and percentage for patients will be presented for following endpoints.

- Patients with biopsy-proven acute allograft rejection. The results will be provided by severity (adjudicated Banff classification)
- Patients using immunosuppressive agents, including specific immunosuppressive agents used. The doses, and any changes in dose will be listed.
- Patients with kidney injury requiring hemodialysis
- Patients with hospitalizations/re-hospitalizations for any reason

The use of antiviral therapies will be listed as concomitant medications but not summarized.

The analyses for all the efficacy endpoints are summarized in Table 1:

Table 1: Efficacy Endpoints Summary and Statistical Analysis

Type of Endpoint	Summary Table
	Population | Variables[*]/Method
Continuous	
• BK viral load	Observed/Chg/Pchg
• eGFR by MDRD	Observed/Chg/Pchg
• eGFR by Creatinine-cystatin C	Observed/Chg/Pchg
Time to event [#]	
• Time to BKV resolution	Kaplan-Meier
• Duration of BKV remission	Kaplan-Meier
Category	
• BKV resolution	Categories: Yes/No
• 1 Log10 reduction of BK viral post infusion	Categories: Yes/No
• Patients with screening BK viremia <10,000 copies/mL develop BK viremia ≥10,000 copies/mL	Categories: Yes/No
• Donor specific anti-HLA antibodies	Categories: Yes/No
• eGFR >20 mL/min/1.73m^2	Categories: Yes/No
• New viral infection	Categories: Yes/No
• Immunosuppression reduction	Categories: Yes/No
• Immunosuppressive agents	Categories: agent type
• Biopsy-proven acute allograft rejection	Categories: severity
• Kidney injury requiring hemodialysis	Categories: Yes/No
Category and continuous	
• Hospitalizations/re-hospitalizations	Yes/No; Duration

N/A = Not Applicable.
[*] Chg = Change from Baseline; Pchg = Percent Change from Baseline.
[$] Line plot will be generated.
[#] Kaplan-Meier plot will be generated for each endpoint.
[**] Ratio is defined as unique clonotype donor DNA/patient DNA*100.

3.5 Safety Analyses

Safety data will be summarized by treatment group (i.e., PSL, Placebo and Overall). Safety summary tables will be generated for actual treatment received, based on the Safety Population. The primary objective of the study is to assess the safety and tolerability of PSL in kidney transplant recipients based on TEAEs and changes in vital signs, physical examinations, clinical laboratory assessments, and ECGs. Categorical endpoints will be summarized using the number and percentage of patients within each category. Continuous endpoints will be summarized descriptively with summary statistics (number, mean, standard deviation, standard error, median, first quartile, third quartile, minimum, and maximum).

3.5.1 Adverse Events

All AEs will be coded to system organ class and preferred term using MedDRA. TEAEs are defined as AEs with a start date and time on or after the first dose of study treatment through

the end of the study. Adverse events of special interest (AESI) include infusion-related AEs, GVHD (graft versus host disease), and CRS (cytokine release syndrome).

An overall summary of AEs will be produced for the following by treatment group. The numbers and percentages of patients will be provided for the following:

- Any TEAEs
- Any TEAEs by severity
- Any treatment-related TEAEs
- Any TEAEs of special interest (AESIs): graft versus host disease, infusion reaction and/or cytokine release syndrome.
- Any treatment-related TEAESIs
- Any serious AEs (SAEs)
- 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

The summaries of above TEAE categories by system organ class (SOC) and preferred term (PT). In addition, TEAE and TESAEs will be summarized by PT (descending frequency). TEAEs, TESAEs, and TEAESIs will also be summarized by severity.

Patients with multiple AEs will be counted only once per SOC and PT. The number and percentage of patients with TEAEs will be tabulated by the highest CTCAE Grade.

Listings will be presented for all AEs, any deaths, SAEs, AESI, and TEAEs leading to discontinuation of study treatment and study.

3.5.2 Clinical Laboratory Tests

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

Descriptive statistics will be provided for clinical laboratory test results (hematology, clinical chemistry and routine urinalysis) and changes from baseline. With the exception of the LOCF sensitivity analysis of BK viremia, missing values for any of the laboratory evaluations will not be imputed; that is, only observed case data will be used.

A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline value according to the NCI CTCAE grade, will be provided for clinical laboratory.

In addition, the number and percentage of patients with the following potentially clinically significant abnormal liver function tests will be summarized:

- Potential Hy's Law cases: ALT or AST ≥3xULN and total bilirubin ≥2xULN and Alkaline phosphatase (ALP) < 2xULN.

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

In addition, other laboratory tests, including pregnancy test, serology test, testing for HIV, HCV, HBV and CMV, and donor specific anti-HLA antibodies will be presented in by-patient listings.

3.5.3 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 treatment group at each scheduled visit. Changes from baseline will also be summarized.

All vital sign data will be listed by patient.

3.5.4 Electrocardiograms

ECG measurements include heart rate (bpm), measures PR (msec), QRS (msec), QT (msec), and QTc (msec) (corrected using Fridericia's and Bazett's methods). Descriptive statistics will be provided for the observed measurements and change from baseline.

All ECG parameters and the Investigator interpretation of findings including details of any abnormalities will be listed by patient.

3.5.5 Physical Examinations

All abnormal physical examination findings, including details of any abnormalities will be listed by patient.

3.6 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 to stop the study or either arm early. The DSMB will receive summary reports of all unexpected SAEs. A DSMB charter, detailing all aspects of the DSMB's composition, scope of review, and procedures will be provided in a separate document. In addition, the DSMB will review safety data after the first 3 patients enrolled have received their 3rd dose.

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.

APPENDIX A: SCHEDULE OF ACTIVITIES

Table 2: Schedule of Activities in Period 1 (Weeks -2 to 12)

At the discretion of the Investigator, and with the exception of Weeks 8 and 12 (which must be conducted at the site), study visits for patients who have undetectable BK plasma viral load at 2 or more consecutive assessments at least 2 weeks apart after 3 doses may be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider. These visits may be conducted via video or telephone call.

Study Week	Weeks -2 to -1	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Study Day	**-14 to -1**	**1[1]**	**8**	**15**	**29**	**43**	**57**	**71**	**85**
Visit Window (Days)	**NA**	**NA**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Study Procedures									
Informed consent[2]	X								
I/E criteria	X	X							
Demographics	X								
Medical history	X								
Prior & concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events[3]	X	X	X	X	X	X	X	X	X
Complete physical examination[4]	X	X							X
Targeted physical examination[4]			X	X	X	X	X	X	
Weight and height[5]	X	X			X		X		X
Vital signs[6]	X	X	X	X	X	X	X	X	X
12-lead ECG[7]	X	X[7]		X[7]					
Documentation of HLA typing[8]	X								
Clinical labs[9]	X	X		X	X	X	X	X	X
Testing for HIV, HCV, and HBV[22]	X								
BKV plasma viral load[10,11]	X	X		X	X	X	X	X	X
Urine for biomarker[12]		X			X		X		X
AdV, CMV, JCV, HHV-6 plasma, and EBV viral load[10]		X			X		X		X
Pregnancy test	X[13]	X[14]			X[14]		X[14]		X[14]
FSH[15]	X								
Randomization[16]		X							
Provide patient cards		X							
Study treatment administration[17]		X	X	X	X	X	X	X	X

Study Week	Weeks -2 to -1	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Study Day	**-14 to -1**	**1[1]**	**8**	**15**	**29**	**43**	**57**	**71**	**85**
Visit Window (Days)	**NA**	**NA**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Post infusion monitoring[18]		X	X	X	X	X	X	X	X
Banked PBMCs for virus specific immunity[19]	X			X	X	X	X		X
Blood for donor DNA[20]					X				X
Kidney biopsy pathologic specimens for review (if clinically indicated)[23]	X	X	X	X	X	X	X	X	X
Donor-specific antibodies [24]		X							X

1. Unless noted otherwise, the Day 1 procedures must be performed within 96 hours of randomization and prior to study treatment administration.
2. Prior to conducting any study-related activities, written informed consent to participate in the study must be provided by the patient.
3. Adverse events will be monitored and documented from randomization through Week 24 in all patients.
4. Complete physical examinations require the patient to be at the site, and will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Targeted physical examinations or assessments will include careful skin examination for GVHD, and other aspects as clinically indicated.
5. Height and weight will be measured at screening; only weight will be measured at other specified later visits. For home visits, stated weight may be used.
6. Includes body temperature, blood pressure, heart rate, and respiration rate and will be measured after resting for 5 minutes. For visits with infusions, vital signs will be measured within 30 minutes prior to infusion, at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. A ±5 minute window will be permitted for all vital sign assessments.
7. Performed within 1 hour after study treatment administration and at the end of study or early termination visit. ECGs will be obtained with the patient in a semi-supine position after a 5-minute rest.
8. The HLA type of the patient and their donor kidney will be obtained from the medical record.
9. CBC must include differential and LFTs must include alkaline phosphatase, bilirubin, AST, and ALT. Urinalysis must be performed.
10. Viral loads of BKV in plasma will be measured. The results of analyses from screening must be available at the time of randomization. Results of central laboratory testing for viral load will be used for the purpose of determining eligibility/inclusion. Additional post-infusion samples may be collected, as clinically indicated. AdV, CMV, JCV, EBV, and HHV-6 viral loads will also be assessed. A whole blood or plasma BK viral load from the local laboratory may be used for the patient to qualify for screening if obtained ≤90 days before the start of screening and with any positive BK viral load (may be reported as either copies/mL or IU/mL).
11. Viral DNA isolated from blood samples will be stored for potential future sequencing/genotyping from the samples collected at baseline for viral load determination. Viral sequencing/genotyping will also potentially be performed in the event of viral recurrence and this sequencing result be compared with the baseline results.
12. Urine samples will be obtained and will be stored for urinary polyomavirus haufen testing.
13. A serum pregnancy test will be performed at screening for all patients of childbearing potential.
14. A urine pregnancy test will be performed at the site prior to study therapy initiation for patients of childbearing potential. If the result is negative, the patient will be eligible for study treatment administration and the remainder of the Day 1 testing/procedures will be performed. If the urine pregnancy result is positive, the patient must not receive study treatment. An on-site urine pregnancy test will also be performed at Weeks 4, 8, and 12 for patients of childbearing potential who are eligible for dosing. Dosing may only be completed following a negative test.

15. FSH will be tested at screening for women of nonchildbearing potential who are postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause.
16. Randomization will occur after all screening procedures are complete, after all eligibility criteria are met, and prior to study treatment administration. Randomization will mark the end of the screening period. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to receive sequential infusions of PSL cells or placebo.
17. Patients will receive infusions of either PSL or placebo after all blood drawing procedures listed for their visit in the SoA. Patients in the active treatment arms will receive the same [redacted] dose for all infusions. Placebo infusions will be administered as appropriate to maintain the blind. As GVHD and CRS are a theoretical safety concern, the incidence and severity of GVHD and CRS will be monitored during the study. No patients are permitted to receive an infusion of PSL or placebo if they develop GVHD (≥Stage 1; see Appendix 5, Section 10.5 of the protocol) or CRS >Grade 2. If any patient develops GVHD or CRS >Grade 2, study treatment infusions should be stopped immediately, and the patient treated per standard of care.
18. Patients will be monitored closely and must remain in the clinic for □1 hour after the end of each infusion. Vital signs, including body temperature, heart rate, respiration rate, and blood pressure, will be measured within 30 minutes prior to infusion, at the end of the infusion, and at 15, 30, 45, and 60 minutes after the end of the infusion. A ± 5 minute window is permitted for all vital sign measurements. Patients must also remain on continuous pulse oximetry for □30 minutes after the end of the infusion. Post-infusion monitoring should be completed for all infusions of study treatment.
19. Blood will be collected into a cell separation tube and processed to generate a PBMC fraction and a plasma fraction. These fractions will be cryopreserved for potential future evaluation of virus-specific T cell immune function/virus-specific T cell persistence and for potential future evaluation of cytokines and/or other humoral markers of inflammation and/or immune function. In addition, a tube of whole blood will be collected for exploratory determination of virus-specific- T cell immune function in whole blood.
20. Blood will be obtained for (virus-specific T cell) donor DNA quantitation at Weeks 4, 12 and 24. Week 24 DNA may not be quantitated, depending on earlier results.
21. Week 24 procedures should be performed on any patient who terminates the study early before Week 24.
22. Serum will be screened for HIV, HBV and HCV antibodies with reflex nucleic acid testing of plasma.
23. Severity of Biopsy (for clinical indication) Proven Acute Rejection will be adjudicated by a blinded review via expert pathologists. No biopsies are required per the protocol.
24. Donor-specific antibody results should be derived from samples sent to the central laboratory.

Abbreviations: AdV = adenovirus; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BKV = BK viremia; CBC = complete blood count; CMV = cytomegalovirus; CRS = cytokine release syndrome DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; ECG = electrocardiogram; ET = Early Termination Visit; FSH = follicle-stimulating hormone; GVHD = graft versus host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HHV-6 = human herpesvirus 6; HLA = human leucocyte antigen; I/E = inclusion and exclusion; JCV = JC virus; LFT = liver function test; NA = not applicable; PBMC = peripheral blood mononuclear cell; PSL=posoleucel; SoA = Schedule of Activities

Table 3: Schedule of Activities in Period 2 (Weeks 14 to 24; Follow-Up Period)

At the discretion of the Investigator, all study visits during Period 2 may be conducted by a Sponsor-approved home health vendor in conjunction with a Sponsor-approved telehealth provider. These visits may be conducted via video or telephone call.

Study Week	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24/ET [1]
Study Day	99	113	127	141	155	169
Visit Window (Days)	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days
Study Procedures						
Prior & concomitant medications	X	X	X	X	X	X
Adverse events[3]	X	X	X	X	X	X
Targeted physical examination[4]	X	X	X	X	X	X
Weight[5]		X		X		X
Vital signs[6]	X	X	X	X	X	X
12-lead ECG[7]						X
Clinical labs[9]		X		X		X
BKV plasma viral load[10,11]	X	X	X	X	X	X
AdV, CMV, JCV, EBV, and HHV-6 plasma viral load[10]		X		X		X
Banked PBMCs for virus-specific immunity[19]		X		X		X
Blood for donor DNA[20]						X
Obtain any clinically indicated kidney biopsy pathologic specimens for review[23]	X	X	X	X	X	X
Donor-specific antibodies[24]						X

See footnotes and abbreviations following Table 3.

APPENDIX B: ANALYSIS VISIT WINDOWS

Table 1. Analysis Visit Windows for Physical Exams and Vital Signs

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1	1	1
Week 1	8	2	11
Week 2	15	12	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	106
Week 16	113	107	120
Week 18	127	121	134
Week 20	141	135	148
Week 22	155	149	162
Week 24	169	>162	

Table 2. Analysis Visit Windows for BK Viral Loads

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1	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	106
Week 16	113	107	120
Week 18	127	121	134
Week 20	141	135	148
Week 22	155	149	162
Week 24	169	>162	

Table 3. Analysis Visit Windows for Clinical labs

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1	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	99
Week 16	113	100	127
Week 20	141	128	155
Week 24	169	>155	

Table 4. Analysis Visit Windows for Non BK viruses

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1	1	1
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	127

Week 20	141	128	155
Week 24	169	>155	

Table 5. Analysis Visit Windows for ECG data

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1/Baseline	1	1	1
Week 2	15	2	92
Week 24	169	>92	