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STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of NPC-21 for Kidney Transplant Recipients at High-Risk of Cytomegalovirus Infection (LionHeart21)
Protocol Number:	NPC-21-2
Protocol Version/Date:	Version 5.0/18 October 2021
Investigational Product:	NPC-21
Sponsor:	Nobelpharma Co., Ltd. NMF Kayabacho Bldg., 1-17-24, Shinkawa Chuo-ku, Tokyo 104-0033, Japan Telephone: +81-3-6670-3800 Fax: +81-3-6670-3801
SAP Version/Date:	Version 1.0/29 March 2023

SIGNATURE PAGE

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

Signature	**Date**
[redacted]	
[redacted]	
[redacted]	
[redacted]	

VERSION HISTORY

Version	Version Date	Description
1.0	29 March 2023	Original signed version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESIs	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Lower Limit of Quantification
CMV	Cytomegalovirus
COVID-19	Coronavirus Disease 2019
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiograms
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Questionnaire
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI	National Cancer Institute
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
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 for Nobelpharma Co., Ltd. protocol NPC-21-2 (Version 5.0; 18 October 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 assess the efficacy and safety of NPC-21 when administered prophylactically to cytomegalovirus (CMV) seronegative patients receiving a first kidney transplant from a CMV seropositive donor.

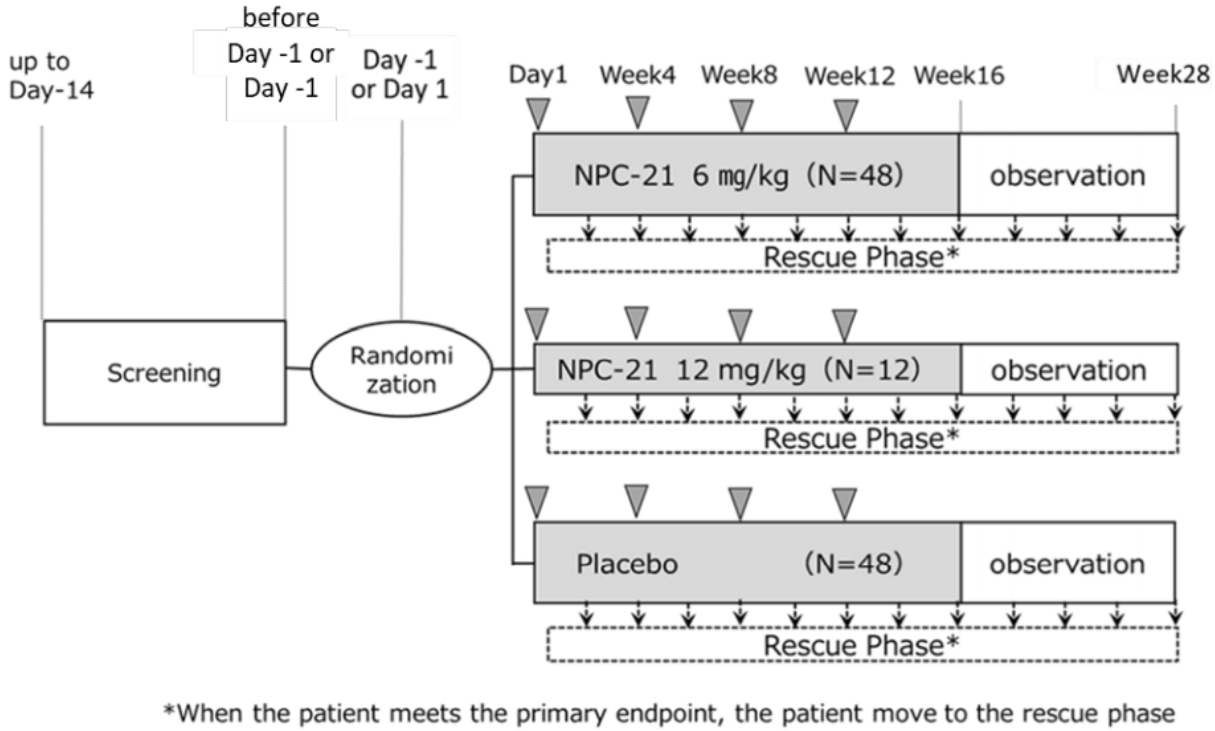
2.2 Study Design

2.2.1 Overview

This is a Phase 2, randomized, double-blind, placebo-controlled study of NPC-21 for kidney transplant recipients at high risk of CMV infection at approximately 25 clinical sites in the United States and Japan. Approximately 108 eligible patients will be randomized in a 4:1:4 ratio prior to first study drug administration to receive 6 mg/kg NPC-21, 12 mg/kg NPC-21, or placebo. Randomization will be stratified by region (United States or Japan).

Figure 1 displays a schematic of the study's design.

Figure 1. Study Schematic



Adult CMV seronegative patients receiving a first kidney transplant from CMV seropositive donors will be enrolled in the study. Participation in the study will consist of a Screening Period (up to 14 days prior to first study drug administration), a 16-week Treatment Period, and a 12-week Observation Period. The total duration of the study (including Screening, Treatment Period, and Observation Period) will be approximately 30 weeks. After first study drug administration, patients who develop detectable CMV disease (CMV syndrome or tissue-invasive CMV disease) or CMV viremia (defined as the detection of ≥250 IU/mL in plasma measured by polymerase chain reaction [PCR] analysis in central laboratory or meets the local criteria for CMV viremia measured by PCR analysis or antigenemia testing) can enter the Rescue Phase of the study and be treated by anti-CMV agents per local standard of care until the patient is negative for CMV viremia, has recovered from CMV disease, or up to Week 28, whichever comes first. When this rescue therapy is completed, the Rescue Phase is terminated at least 4 Study Weeks after the last study drug administration and all Week 28 procedures will be performed as per Section 6.7 the Early Termination Visit and Withdrawal Procedures of the protocol.

The 16-week Treatment Period will include study drug administration on Day 1 and at Weeks 4, 8, and 12. The 16-week Treatment Period will begin as soon as practical post-transplant but no later than 7 days post-transplant.

Blood samples will be collected at Screening; prior to study drug administration on dosing days (Day 1 and at Weeks 4, 8, and 12); and at Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, and 28 for CMV deoxyribonucleic acid (DNA) analysis utilizing PCR analysis or CMV antigenemia testing. The central laboratory will perform CMV PCR analysis, and the local laboratory will perform CMV PCR analysis or CMV antigenemia testing consistently throughout the study. Upon entering the Rescue Phase, a blood sample will be collected for CMV DNA analysis utilizing PCR analysis performed by the central laboratory.

Blood samples for anti–NPC-21 antibody testing will be collected prior to study drug administration on dosing days (Day 1 and at Weeks 4, 8, and 12) and at Weeks 16 and 28.

Blood samples that will be stored for screening for resistant strains analysis will be collected prior to study drug administration on Day 1 and at Weeks 16 and 28 and at the initiation of the Rescue Phase.

Blood samples for serum NPC-21 concentration measurements will be collected within 2 hours prior to study drug administration and at 2 hours (±30 minutes) following the beginning of the infusion on dosing days (Day 1 and at Weeks 4, 8, and 12) and at Weeks 1, 2, 3, 6, 10, 14, 16, 20, 24, and 28 (Note: Sample collection time points at each visit may be updated based on each administration data).

The EuroQol 5 Dimensions 5 Levels questionnaire (EQ-5D-5L) will be performed prior to study drug administration on Day 1, at Weeks 16 and 28, and at the initiation of the Rescue Phase.

The safety of NPC-21 in CMV seronegative patients will be evaluated through physical examination findings, 12-lead electrocardiograms (ECGs), vital signs, changes in clinical laboratory assessments (blood biochemistry [including liver function tests and enzymes], hematology [including complete blood count with differential], coagulation, and urinalysis), and adverse event (AE) monitoring.

2.2.2 Randomization

At Screening, a unique patient identification number will be established for each patient who has provided written informed consent. This patient identification number will be used for patient identification throughout the study and in all study-related documentation. This will be a 5 digit hyphenated number of the following format: XYY-ZZ, where X is the country number (1 [US] or 2 [Japan]), YY is the sequential unique site identification number, and ZZ is a sequential unique number assigned to the patient at that site.

Each patient number will be assigned only once and will not be reassigned to another patient if a patient fails during Screening. Interactive Response Technology (IRT) will not allow repeat of numbers. This unique identifier will be used in all study documentation for that patient from first to last contact.

After informed consent and body weight are obtained, pre-Randomization will take place via the IRT system to 1 of 3 treatment groups (6 mg/kg NPC-21, 12 mg/kg NPC-21, or placebo) in a 4:1:4 ratio. Randomization will be stratified by region (United States or Japan). Randomization will take place prior to first study drug administration after confirming all criteria. Randomization procedures may occur on Day -1 or Day 1 prior to first study drug administration.

2.2.3 Study Drug

[redacted] Normal saline supplied by [redacted] will be used as the placebo.

2.2.4 Sample Size Determination

A total sample size of approximately 108 patients is planned for the study, with a 1:1 randomization ratio for 6 mg/kg NPC-21 versus placebo and another 12 patients for high-level dose of 12 mg/kg NPC-21 (4:1:4 randomization ratio for 6 mg/kg NPC-21, 12 mg/kg NPC-21, or placebo). The sample size calculation is based on the modified Intent-to-Treat (mITT) Population from the first dose of NPC-21 through Week 16 for the occurrence of CMV disease (CMV syndrome or tissue-invasive CMV disease) or CMV viremia (defined as the detection of ≥ 250 IU/mL in plasma measured by PCR analysis in central laboratory or meets the local criteria for CMV viremia measured by PCR analysis or antigenemia testing) primary endpoint. Assuming an early discontinuation rate of 15%, approximately 48 patients each in the 6 mg/kg NPC-21 and placebo arms are needed with a 2-sided significance level of 0.05 and a power of 80% to detect a difference between NPC-21 at a predicted incidence rate of CMV disease (CMV syndrome or tissue-invasive CMV disease) or CMV viremia of 30% versus 60% for placebo. In addition, a sample size of 12 patients for the 12 mg/kg NPC-21 arm is considered adequate for the planned exposure-response analysis.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the incidence of CMV disease (CMV syndrome [see Appendix C of protocol for definition of CMV syndrome] or tissue-invasive CMV disease [see Appendix D of protocol for definitions of CMV disease]) or CMV viremia (defined as the detection of ≥ 250 IU/mL in plasma measured by PCR analysis in central laboratory or meets the local criteria for CMV viremia measured by PCR analysis or antigenemia testing) by Week 16.

2.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Incidence of CMV disease or CMV viremia by Week 28
- Incidence of CMV disease
- Incidence of CMV viremia

- Time to detectable CMV disease or CMV viremia
- Time to detectable CMV disease
- Time to detectable CMV viremia
- Amount of CMV DNA by PCR analyzed by the central laboratory
- Incidence and duration of anti-CMV therapy during the Rescue Phase
- Changes in EQ-5D-5L score from Baseline to Weeks 16 and 28

2.3.3 EuroQol 5 Dimensions 5 Levels Questionnaire

EQ-5D-5L is developed by EuroQol Research Foundation and is a measure of health-related quality of life. It consists of two elements, 5-item questionnaire and EQ-Visual Analogue Scale. EQ-5D-5L is a version that further improves sensitivity of EQ-5D-3L and that provides respondents with a wider range of options to describe their health, which has five response levels.

- 5-Item Questionnaire: The questionnaire provides a simple descriptive profile of health state. The questionnaire comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and each dimension has 5 response levels (1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, 5-unable to/extreme problems).

2.3.4 Safety Endpoints

The safety of NPC-21 in CMV seronegative patients will be evaluated through physical examination findings, 12-lead ECGs, vital signs, changes in clinical laboratory assessments (blood biochemistry [including liver function tests and enzymes], hematology [including complete blood count with differential], coagulation, and urinalysis), and AE monitoring.

Events of serious hypersensitivity that are Grade 3 or higher or lead to treatment discontinuation will be monitored as AEs of special interest (AESIs) during this study. During the course of the study, vacuolization associated with immunoglobulin will be added as AESIs, and additional AESIs may be identified by the Sponsor.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

The low analysis day of the analysis window will be calculated as the midpoint between the scheduled assessment and previously scheduled assessment for that parameter. The high analysis day of the analysis window will be calculated as the midpoint between the scheduled assessment and the next scheduled assessment for that parameter. Within each analysis visit, scheduled visits will be assigned to the analysis visit. If a scheduled visit is not available, unscheduled and early termination visits will be assigned to analysis visits using analysis visit windows based on the actual date the assessment took place.

Where multiple measurements for a particular parameter appear within an analysis window, the scheduled visit will be used. If no scheduled visit appears in the analysis window, the result closest to the target day will be used. If equidistant and both are unscheduled and/or early termination visits, the later result will be used for the summary measure. Specially, if patients do not receive the study drug at scheduled visit (e.g.,

Day 29) but receive the study drug within this visit window and record as "Unscheduled", the results close to this unscheduled visit will be used if there are both results for scheduled visit and unscheduled visit. The analysis visit table below is applicable for both safety and efficacy analysis.

Analysis Visit	Target Day	Low Analysis Day	High Analysis Day
Baseline	1	Null	1
Day 8	8	2	11
Day 15	15	12	18
Day 22	22	19	25
Day 29	29	26	32
Day 36	36	33	39
Day 43	43	40	46
Day 50	50	47	53
Day 57	57	54	60
Day 64	64	61	67
Day 71	71	68	74
Day 78	78	75	81
Day 85	85	82	88
Day 92	92	89	95
Day 99	99	96	102
Day 106	106	103	109
Day 113	113	110	116
Day 120	120	117	123
Day 127	127	124	130
Day 134	134	131	137
Day 141	141	138	144
Day 148	148	145	151
Day 155	155	152	158
Day 162	162	159	165
Day 169	169	166	176
Day 183	183	177	189
Day 197/ET	197	190	200

3.1.3 Definition of Baseline

Baseline is defined as the last non-missing measurement prior to the first dose of study drug. Both date and time will be considered in baseline derivation. Measurement from Day 1 prior to study drug administration will be used. If not available, the last non-missing measurement prior to Day 1 will be used.

3.1.4 Summary Statistics

Summary statistics will be presented by treatment group. Unless otherwise stated, continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized by using the frequency count and the percentage of patients in each category as descriptive statistics. 95% confidence intervals will be provided for categorical efficacy endpoints.

For time-to-event variables, the Kaplan-Meier method will be used to estimate the median time (weeks) and its 95% confidence interval.

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.

In case the start and end dates for AEs 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 electronic case report forms (eCRFs) will be presented in the data listings.

All central CMV DNA PCR values will be used for the efficacy analyses and the local laboratory values will be listed. For the calculation of descriptive statistics of central CMV DNA results, below the lower limit of quantification (BLQ) values will be set to zero if result is reported as "< 102" with unit "IU/mL". Missing data reported as "quality not sufficient" will not be imputed.

Changes in study visit schedules, missed or delayed visits, or patient discontinuations and the relationship to COVID-19 will be captured in the eCRFs.

3.2 Analysis Populations

3.2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all randomized patients.

3.2.2 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) Population will include all patients who receive a kidney transplant from a living or deceased donor and receive at least 1 dose of study drug (6 mg/kg NPC-21, 12 mg/kg NPC-21, or placebo). The mITT Population will be used for all efficacy analyses.

3.2.3 Per Protocol Population

The Per Protocol (PP) Population will include all patients in the mITT Population who have no major protocol deviations. PP Population will be used for primary endpoint analyses. Major protocol deviations that may impact the primary efficacy assessment may include but are not limited to:

- Failed to meet eligibility criteria at randomization
- The first dose of study drug was not administered within 7 days of the kidney transplant
- The study treatment was administered out of the protocol allowed window
- Failed to receive the study treatment at scheduled visit
- Failed to complete the infusion and underdosed
- Took the wrong study drug (i.e., did not take the randomized study drug)
- Used a restricted concomitant medication not permitted per protocol
- Any other major protocol deviations

A list of subjects with major protocol deviations leading to exclusion from the PP Population will be finalized prior to unblinding the randomized treatment assignments.

3.2.4 Pharmacokinetic Population

The Pharmacokinetic (PK) Population will include all patients who receive any amount of study drug (6 mg/kg NPC-21, 12 mg/kg NPC-21, or placebo) and have evaluable PK data. The PK Population will be used for the PK analyses and exposure-response analyses.

3.2.5 Safety Population

The Safety Population will include all randomized patients who receive at least 1 dose of study drug (6 mg/kg NPC-21, 12 mg/kg NPC-21, or placebo). The Safety Population will be used for safety analyses.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

The following patient disposition categories will be summarized via counts and percentages by treatment group and in total for all screened patients:

- Patients who were screened
- Patients who were randomized
- Patients who were treated
- Patients who end study treatment and continued in the study for assessments
- Patients who end study treatment but discontinued in the study for assessments
    - Primary reason for discontinuation
- Patients who completed the study
- Patients who withdrew early from the study
    - Withdrew early from the study before Week 16
    - Withdrew early from the study after Week 16
    - Primary reason for early withdrawal
- Patients who entered rescue phase
    - Reason for entering rescue phase

All patient disposition data will be listed by-patient.

3.3.2 Protocol Deviations

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

Protocol deviations in study procedures due to COVID-19 will be reported in the CSR. All protocol deviations data will be listed by-patient.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment group and in total based on all randomized patients.

All analysis population data will be listed by-patient.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Country (United States, Japan)

- Age (Years)
- Age group (< 65, ≥ 65)
- Sex (Male, Female)
    - Childbearing potential
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other: Specify)
- Height (cm)
- Weight at pre-randomization (kg)
- Weight group (< 100 kg, ≥ 100 kg)
- Body mass index (kg/m^2)
- Time from transplantation to first dose date(days)
    - Day = First dose date of study drug – date of kidney transplant + 1.
- Primary disease (Diabetic Kidney Disease, Glomerulonephritis, Polycystic Kidney Disease, Other, Not Specified, Unknown)
- Donor status (Deceased, Living)
- ABO compatibility (Compatible, Incompatible)
- Dialysis introduction (Yes, No)
    - Dialysis specify (Hemodialysis, Peritoneal Dialysis)
- Central CMV DNA level (IU/mL) at baseline
- Induction therapy (Yes, No), if yes, summarize by the below categories:
    - Alemtuzumab
    - ATG (Thymoglobulin®)
    - Rituximab
    - Basiliximab
    - Bortezomib
    - Eculizumab
- Immunosuppressive agents at randomization (Azathioprine, Belatacept, Cyclosporine, Everolimus, Gusperimus, MMF, Sirolimus, Steroids, Tacrolimus)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment group and in total for all defined analysis populations.

3.3.5 Medical History

Counts and percentages of patients who experienced any past and/or concomitant diseases, and counts and percentages of patients who experienced any past surgeries will be summarized by treatment group and in total.

Medical history will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) v24.0. Counts and percentages of patients with medical history by SOC and PT will be summarized by treatment group and in total based on Safety Population.

All medical/surgical history data will be listed by-patient.

3.3.6 Prior and Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and PT using the WHODrug Global B3, March 2021. Medications will be considered as prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the

first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing, or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of patients taking prior and concomitant medications by ATC class and PT will be summarized by treatment group and in total based on the Safety Population, separately. Patients will be counted only once by medication class or name.

All prior and concomitant medications will be listed by-patient.

3.3.7 Study Drug Exposure

The duration of study drug will be calculated as:

- Duration of study drug (days) = last dose date of study drug + 28 – first dose date of study drug

Total volume administered (mL):

- Total volume administered (mL) = cumulative volume of study drug administered up to last dose

Total study drug administered (mg):

- Total study drug administered (mg) = 10 × Total volume administered (mL)

Duration of study drug, total study drug administered (mg), and the count and percentages of number of infusions administered (e.g., 1, 2, 3, 4) will be summarized by treatment group.

In addition, for each scheduled visit (e.g., Day 1, Day 29, Day 57, and Day 85), the proportion of patients who receive the treatment among patients who are expected to receive the treatment will be summarized. For each visit, the patients who withdraw from the treatment or enter the rescue phase by this visit will be excluded from the analysis.

All study drug exposure data will be listed by-patient.

3.4 Efficacy Assessment

The mITT Population will be used for efficacy analyses. The primary efficacy endpoint will also be analyzed on the PP Population.

3.4.1 Primary Efficacy Analysis

The proportion of patients with the occurrence of CMV disease (CMV syndrome [see Appendix C of the protocol for definition of CMV syndrome] or tissue-invasive CMV disease [see Appendix D of the protocol for definitions of CMV disease]) or CMV viremia (defined as the detection of ≥ 250 IU/mL in plasma measured by PCR analysis in central laboratory or meets the local criteria for CMV viremia measured by PCR analysis or antigenemia testing) by Week 16 will be summarized by treatment group.

The 2-sided 95% exact Clopper-Pearson confidence intervals of the proportions will be provided. For any two treatment groups, the proportion difference and 95% unstratified Miettinen-Nurminen (score) confidence limits will be presented.

Comparisons across placebo and 6 mg/kg NPC-21 treatment group will use logistic regression analysis with stratification factor of region (United States or Japan) as a covariate

Non-responders will include all patients who develop CMV disease or CMV viremia. In principle, patients who discontinue from the study prior to Week 16 in the absence of CMV disease or CMV viremia will be considered as non-responders. If warranted under special circumstances, a patient who discontinues from the study prior to Week 16 may be discussed with the medical expert to determine status as a responder or non-responder. If this occurs, the rationale for considering the patient as a responder will be finalized before database lock and documented in this SAP. Sensitivity analysis may be performed to assess the impact of these patients on analysis results.

3.4.2 Secondary Efficacy Analysis

3.4.2.1 Categorical Endpoints

The categorical endpoints as below will be analyzed using the same analysis method as primary analysis:

- Incidence of CMV disease or CMV viremia by Week 28
- Incidence of CMV disease by Week 16
- Incidence of CMV disease by Week 28
- Incidence of CMV viremia by Week 16
- Incidence of CMV viremia by Week 28
- Incidence of anti-CMV therapy during the Rescue Phase

3.4.2.2 Continuous Endpoints

Descriptive statistics will be presented by treatment group for the continuous endpoints as below:

- Amount of CMV DNA by PCR analyzed by the central laboratory
    - Descriptive statistics will be provided for amount of CMV DNA (IU/mL) at each scheduled visit and changes from baseline will be presented as well.
- Duration of anti-CMV therapy during the Rescue Phase
- Duration of the detection of CMV DNA ≥ 250 IU/mL in plasma measured by PCR analysis in central laboratory
- Changes in EQ-5D-5L score from Baseline to Weeks 16 and 28
    - Counts and percentages of patients with each of five response levels in each domain will be presented by treatment and visit.
    - Changes from baseline for total health status will be presented as well.

3.4.2.3 Time-to-Event Endpoints

The time-to-event endpoints include:

- Time to detectable CMV disease or CMV viremia by Week 28
- Time to detectable CMV disease by Week 28
- Time to detectable CMV viremia by Week 28

For each time-to-event endpoint, the count and proportion of patients experiencing event and censored will be summarized by treatment group. The Kaplan-Meier estimate of median time and Brookmeyer-Crowley 95% confidence intervals will be presented. Log-rank test will be used to test whether there is significant difference among groups.

The endpoints will be calculated as:

- Time to detectable CMV disease or CMV viremia by Week 28 (Weeks) = (Date of CMV disease or CMV viremia – first dose date of study drug + 1)/7.
- Time to detectable CMV disease by Week 28 (Weeks) = (Date of CMV disease – first dose date of study drug + 1)/7.
- Time to detectable CMV viremia by Week 28 (Weeks) = (Date of CMV viremia – first dose date of study drug + 1)/7.

If patients experience CMV disease or CMV viremia, the dates of entering Rescue Phase will be used to determine the date of CMV disease or CMV viremia and the patients will not be censored. Patients who do not experience CMV disease or CMV viremia will be censored at the latest CMV viremia assessments.

3.4.3 Exploratory Analysis

As the exploratory analysis, incidence of CMV disease or CMV viremia by Week 16 assessed by Endpoint data reviewers will be analyzed using the method described in Section 3.4.1. In addition, the below endpoints will also be analyzed.

- Incidence of CMV disease or CMV viremia by Week 28
- Incidence of CMV disease by Week 28
- Incidence of CMV viremia by Week 28

In addition, the Endpoint data reviewer findings will be listed by-patient.

As the supportive analysis, only criteria using the detection of ≥ 250 IU/mL in plasma measured by PCR analysis in central laboratory will be considered for the analysis of primary efficacy endpoint in Section 3.4.1. Non-responders will include all patients who have central CMV DNA assessments ≥ 250 IU/mL by Week 16. Patients who discontinue from the study prior to Week 16 in the absence of central CMV DNA assessments ≥ 250 IU/mL will be considered as non-responders.

3.4.4 Subgroup Analysis

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

Statistical analysis of the primary efficacy endpoint and selected secondary efficacy endpoints will be provided within each category of the following variables if the data allows:

- Country (United States, Japan)
- Weight group (< 100 kg, ≥ 100 kg)
- ABO compatibility (Compatible, Incompatible)
- Induction therapy (Yes, No)
- Donor status (Deceased, Living)

3.5 Analysis of Pharmacokinetic

Serum concentrations of NPC-21 will be summarized using descriptive statistics. Geometric mean and geometric coefficient of variation will also be provided. For the calculation of descriptive statistics, BLQ values will be set to zero and missing data will not be imputed. 2-hour post-dose samples collected outside the sampling window of 2 hours +/- 30 minutes after infusion start may be excluded from the calculation of descriptive statistics. Plots of mean concentrations of plasma NPC-21 versus time will be generated for each dose group and scheduled visit.

In addition, analysis of the concentration data as part of population-PK modeling will be described in a separate PK Analysis Plan and reported separately.

The PK listing will be provided.

3.6 Analysis of Exposure-Response

Exposure-response analyses will be performed to propose target concentrations using PK parameters estimated by population-PK, efficacy variables, and biomarker, which will be described in a separate analysis plan.

3.7 Safety Assessment

The Safety Population will be used for all safety analyses. Safety will be summarized descriptively by treatment group.

Descriptive summary statistics will be provided for all safety variables, including 12-lead ECGs, vital signs, clinical laboratory assessments, and AEs reported during the study.

3.7.1 Adverse Events

AEs will be monitored and documented from the time informed consent is obtained until Week 28. All AEs will be coded using MedDRA v24.0.

Treatment-emergent AEs (TEAEs) are defined as AEs that start on or after the first dose of study drug.

Events of serious hypersensitivity that are Grade 3 or higher or lead to treatment study drug discontinuation and vacuolization associated with immunoglobulin will be monitored as AESIs.

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

- Any TEAEs
- Any Grade 3 or higher TEAEs
- Any study drug related TEAEs
- Any study drug related Grade 3 or higher TEAEs
- Any AEs related to anti-CMV rescue medication
- Any AESIs
- Any Grade 3 or higher AESIs
- Any SAEs
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death
- Any AEs related to COVID-19

Numbers and percentages of patients will also be presented by SOC and PT for each category in the summary tables.

Listings will be presented for AEs, Grade 3 or higher AEs, SAEs and TEAEs leading to discontinuation of study drug.

3.7.2 Clinical Laboratory Evaluations

Standard clinical laboratory profiles for blood biochemistry, hematology, coagulation, and urinalysis will be evaluated at the local laboratory at Screening and at the local laboratory (Japan sites) and central laboratory (US sites) prior to study drug administration on dosing days (Day 1 and at Weeks 4, 8, and 12) and at Weeks 1, 2, 6, 10, 14, 16, 20, 24, and 28. Samples for evaluation by the central laboratory may be collected by home healthcare services at non-dosing day visits. See Appendix B of the protocol for a complete list of laboratory analytes.

Clinical laboratory evaluations will be summarized using descriptive statistics if sufficient data is available for selected laboratory parameters including absolute measurements and changes from baseline by scheduled time of evaluation. Changes from baseline by scheduled time of evaluation will include last analysis visit, maximum post-treatment value, and minimum post-treatment value. Both scheduled and unscheduled post-treatment visits will be considered for the summaries of the maximum and minimum post-treatment values.

Abnormal laboratory results will be graded according to NCI CTCAE v5.0. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline grade according to NCI CTCAE grades, will be provided for selected clinical laboratory tests. For select parameters (e.g. glucose), separate shift tables indicating hyper–and hypo-directionality of change may be produced. The worst post-baseline grade will be derived from all post-baseline visits including scheduled and unscheduled.

The shift table for all parameters will be provided based on the categories Low, Normal and High based on normal ranges. Hyper–and hypo-directionality of change may be produced.

Clinical laboratory evaluations will be listed by-patient. Abnormal values will be flagged.

3.7.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) will be taken in the supine or sitting position after resting at Screening; prior to study drug administration on dosing days (Day 1 and at Weeks 4, 8, and 12); within 1 hour of the end of the infusion on Day 1; and at Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, and 28. Vital signs may be taken by home healthcare services at non-dosing day visits.

Descriptive statistics will be provided for vital signs assessments. Changes from baseline by scheduled evaluation, and maximum and minimum post-treatment values may be presented. Both scheduled and unscheduled post-treatment values will be considered for summaries of the minimum and maximum.

The counts and percentages of patients with the following potentially abnormal vital signs at any post-baseline visits will be summarized:

- Pulse rate < 50 bmp and decrease ≥ 15 bpm from baseline
- Pulse rate > 100 bpm and increase ≥ 15 bpm from baseline
- Systolic blood pressure ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline
- Systolic blood pressure ≥ 140 mmHg and increase ≥ 20 mmHg from baseline
- Diastolic blood pressure ≤ 50 mmHg and decrease ≥ 10 mmHg from baseline
- Diastolic blood pressure ≥ 90 mmHg and increase ≥ 10 mmHg from baseline

Vital signs assessments will be listed by-patient.

3.7.4 Electrocardiograms

A 12-lead ECG will be performed in a supine position after resting at Screening; prior to study drug administration at Weeks 4, 8, and 12; and at Weeks 16, 20, 24, and 28. Additional follow-up ECGs may be performed if clinically indicated. A 12-lead ECG may be performed by home healthcare services at non-dosing day visits.

Overall evaluation of ECG is collected at each visit in terms of

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

The counts and percentages of patients within each category will be summarized by treatment group and visit.

ECG assessments will be presented in a by-patient listing.

3.7.5 Physical Examinations

A complete physical examination will be performed at Screening; prior to study drug administration on dosing days (Day 1 and at Weeks 4, 8, and 12); within 1 hour of the end of the infusion on Day 1; at Weeks 1, 2, 3, 16, 20, 24, and 28; and at the initiation of the Rescue Phase. A physical examination may be performed by home healthcare services at non-dosing day visits.

The physical examination will be presented in a by-patient listing.

3.7.6 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will meet to review unblinded aggregate and individual patient data related to safety, data integrity, and overall conduct of the study and will provide recommendations to continue, temporarily halt, modify, or terminate the study based on data analysis. The committee may communicate other recommendations or concerns as deemed appropriate. Additional information will be provided in the DSMB charter as approved by the members.

3.8 Interim Analysis

No interim analysis is planned.

4 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

In Section 3.4.2.2 for secondary efficacy analysis, the below secondary analysis was added compared to protocol:

- Duration of the detection of CMV DNA ≥ 250 IU/mL in plasma measured by PCR analysis in central laboratory.

The section 3.4.3 was added as the exploratory analysis to the endpoints.

5 PROGRAMMING SPECIFICATIONS

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

[redacted]

STATISTICAL ANALYSIS PLAN ADDENDUM

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of NPC-21 for Kidney Transplant Recipients at High-Risk of Cytomegalovirus Infection (LionHeart21)
Protocol Number:	NPC-21-2
Protocol Version/Date:	Version 5.0/18 October 2021
Investigational Product:	NPC-21
Sponsor:	Nobelpharma Co., Ltd. NMF Kayabacho Bldg., 1-17-24, Shinkawa Chuo-ku, Tokyo 104-0033, Japan Telephone: +81-3-6670-3800 Fax: +81-3-6670-3801
SAP Version/Date:	Version 1.0/29 March 2023
SAP Addendum Version/Date:	Version 1.0/15 May 2023

SIGNATURE PAGE

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of NPC-21 for Kidney Transplant Recipients at High-Risk of Cytomegalovirus Infection (LionHeart21)
Protocol Number:	NPC-21-2
SAP Addendum Version/Date:	Version 1.0/15 May 2023

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

Signature	**Date**
[redacted]	
[redacted]	
[redacted]	
[redacted]	

TABLE OF CONTENTS

1 INTRODUCTION

The statistical analysis plan (SAP), version 1.0, for the study with protocol number NPC-21-2 was finalized on 29 March 2023.

The final database lock for this study was on 30 March 2023 with last signature data lock approval on 03 April 2023. Further updates to the planned analysis are documented in this addendum.

Summary of changes:

- Updated the analysis methods of some secondary and exploratory endpoints

2 DATA ANALYSIS CHANGES

2.1 Categorical Endpoints

In SAP version 1.0, section 3.4.2.1 describes that the categorical endpoints are analyzed using the same analysis method as the primary endpoint.

However, for the analysis of primary endpoint, the non-responders include all patients who develop CMV disease or CMV viremia and patients who discontinue from the study prior to Week 16 in the absence of CMV disease or CMV viremia.

This SAP addendum further clarifies that for the endpoints below, patients who discontinued from the study prior to Week 16 in the absence of CMV disease would not be considered as non-responders:

- Incidence of CMV disease by Week 16
- Incidence of CMV disease by Week 28

For the endpoints below, patients who discontinued from the study prior to Week 16 in the absence of CMV viremia would not be considered as non-responders:

- Incidence of CMV viremia by Week 16
- Incidence of CMV viremia by Week 28

For the secondary endpoint “Incidence of CMV disease or CMV viremia by Week 28”, the same analysis method as the primary endpoint is used by still including patients who discontinued from the study prior to Week 16 in the absence of CMV disease or CMV viremia as non-responders.

2.2 Exploratory Analysis

In SAP version 1.0, the first paragraph of section 3.4.3 describes that the endpoints below are analyzed using the same method as the primary endpoint:

- Incidence of CMV disease or CMV viremia by Week 16
- Incidence of CMV disease or CMV viremia by Week 28
- Incidence of CMV disease by Week 28
- Incidence of CMV viremia by Week 28

This SAP addendum further clarifies that for the endpoint “Incidence of CMV disease by Week 28”, patients who discontinued from the study prior to Week 16 in the absence of CMV disease would not be considered as non-responders.

For the endpoints “Incidence of CMV viremia by Week 28”, patients who discontinued from the study prior to Week 16 in the absence of CMV viremia would not be considered as non-responders.

For the endpoints “Incidence of CMV disease or CMV viremia by Week 16” and “Incidence of CMV disease or CMV viremia by Week 28”, the same analysis method as the primary endpoint is used by still including patients who discontinued from the study prior to Week 16 in the absence of CMV disease or CMV viremia as non-responders.