CLINICAL STUDY PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of NPC-21 for Kidney Transplant Recipients at High-Risk of Cytomegalovirus Infection (LionHeart21)

Investigational Product: NPC-21
Protocol Number: NPC-21-2
IND Number: 145353

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SIGNATURE PAGE

STUDY TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of NPC-21 for Kidney Transplant Recipients at High-Risk of Cytomegalovirus Infection (LionHeart21)

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
_____	_____

[redacted]
Nobelpharma Co., Ltd.

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Nobelpharma Co., Ltd. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Nobelpharma Co., Ltd. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Nobelpharma Co., Ltd., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Independent Ethics Committee Regulations, International Council for Harmonisation Guidelines for Good Clinical Practices, and the Japanese Ministerial Ordinance on Good Clinical Practice for Drugs, where applicable.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

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

INVESTIGATIONAL PRODUCT: NPC-21

PHASE: 2

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.

POPULATION:

Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients 18 to ≤75 (<76) years of age in the United States or 20 to ≤75 (<76) years of age in Japan at the time of obtaining informed consent.
2. Patients must be CMV seronegative pre-transplant and scheduled to receive or have received (within 7 days prior to first study drug administration) a first kidney transplant from a CMV seropositive donor.
3. Patients must be willing and able to give written informed consent for participation in the study.
4. Patients must be eligible to undergo kidney transplantation from a living or deceased donor, as per institutional standards.
5. Female patients of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before Screening) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone in the postmenopausal range at Screening, based on the laboratory's reference range.
6. Female patients of childbearing potential (ie, not postmenopausal or surgically sterilized) must have a negative urine or serum pregnancy test result at Screening. Participating female patients of childbearing potential must agree to use 1 of the following throughout the duration of the study and for 90 days following the last study drug administration:
    - One highly effective method of contraception and an acceptable barrier method (condom used by male partner plus spermicide).
    - Two highly effective methods of contraception.

Investigators will select the appropriate methods of contraception in accordance with local regulatory requirements. Highly effective methods of contraception that result in a low failure rate (ie, <1% per year) when used consistently and correctly include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, or intrauterine hormone-releasing system for at least 12 weeks before Screening.
- Bilateral tubal occlusion or vasectomized partner at least 26 weeks before Screening.

  Note: A vasectomized partner is a highly effective method of contraception, provided that the male partner is the sole sexual partner of the study patient who is a female of childbearing potential and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence.

  Note: True abstinence, when in line with the preferred and usual lifestyle of the patient, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male patients must agree to abstain from sperm donation and use condoms with spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug. Male patients must ensure nonpregnant female partners of childbearing potential comply with the contraception requirements in Inclusion Criterion 6.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Patients who have received a previous solid organ transplantation or hematopoietic stem cell transplantation.
2. Patients who receive a multi-organ transplant.
3. Patients who have CMV disease (CMV syndrome or tissue-invasive CMV disease) or CMV viremia (polymerase chain reaction [PCR] analysis or antigenemia testing in local laboratory meets the local criteria for CMV viremia) at Screening.
4. Patients who have a positive donor-specific antibody within 90 days prior to Randomization confirmed via medical records.
5. Patients whose body weight is more than 120 kg at Screening.

   Note: In case of hemodialysis patients, body weight is defined immediately after dialysis or dry weight. In case of peritoneal dialysis patients, body weight is defined after removal of dialysate or dry weight.

   Note: Body weight measured within 7 days prior to pre-Randomization is permitted.

6. Patients who have received the following anti-CMV therapy within 7 days prior to Randomization and/or plan to receive the following anti-CMV therapy during the study:
   - Anti-CMV agents (eg, foscarnet, ganciclovir, valganciclovir, letermovir, high dose acyclovir [≥500 mg/m^2 intravenously every 8 hours, 10 mg/kg intravenously every 8 hours or 800 mg orally 4 times a day], high dose valacyclovir [1000 mg orally 3 times a day], high dose famciclovir [500 mg orally every 8 hours], or cidofovir).

     Note: The use of anti-CMV agents per local standard of care during the Rescue Phase of the study is permitted.

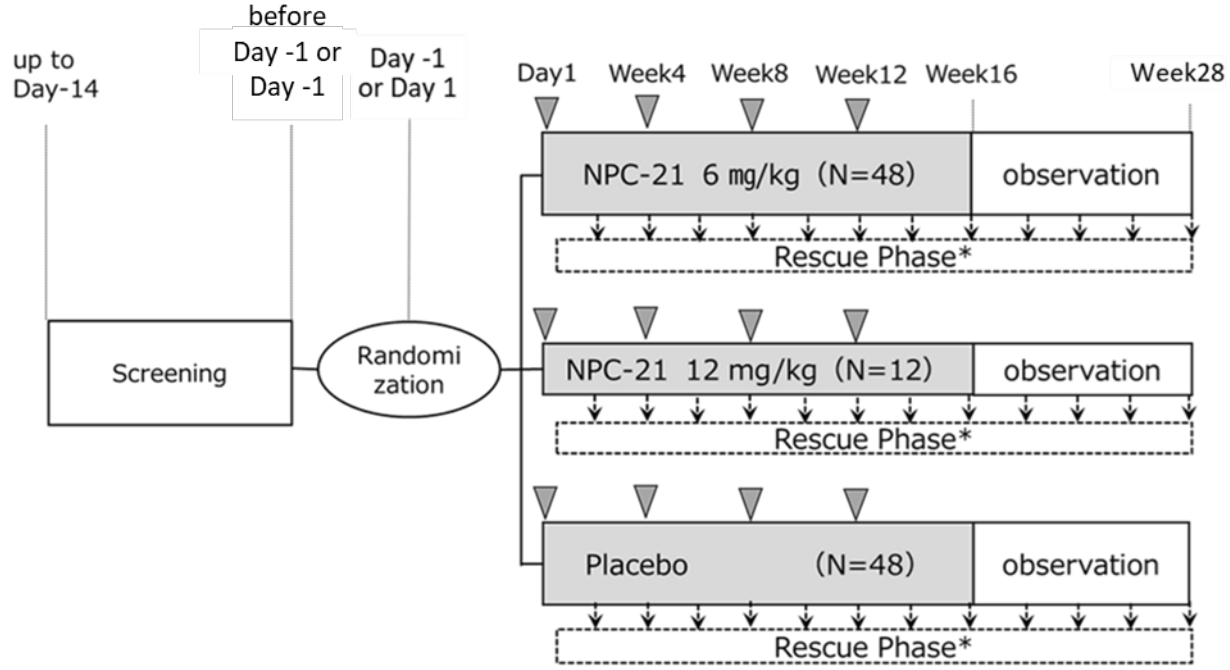
     Note: The use of anti-herpes simplex virus and anti-varicella zoster virus prophylaxis for at-risk patients is recommended (as long as the doses are below the one specified above).
7. Patients who have received the following therapy within 28 days prior to Randomization and/or plan to receive the following anti-CMV therapy during the study:
   - CMV hyperimmune globulin (eg, CytoGam®).
   - Intravenous immunoglobulin.
   - Plasmapheresis (receipt prior to first study drug administration is acceptable).
8. Patients with a history of a serious drug allergy to proteins, immunoglobulins, transfusions, or vaccines or any excipient of the NPC-21 formulation.
9. Patients with severe hepatic insufficiency at Screening (eg, Child-Pugh Class C).
10. Patients with active and untreated hepatitis B virus or hepatitis C virus, as documented as part of the pre-transplant testing.
11. Patients with known human immunodeficiency virus infection, based on medical records serology.
12. Patients with any uncontrolled infection at Randomization or a history of serious and uncontrolled infection within 6 months prior to Randomization.
13. Patients who are pregnant or lactating.
14. Patients with a history of malignancy within 5 years prior to Randomization other than curatively treated in situ cervical carcinoma, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
15. Patients with a history of alcohol or drug abuse or dependence within 1 year prior to Randomization that, in the opinion of the Investigator, would preclude study participation.
16. Patients who have previously participated in this study or any other study involving NPC-21.
17. Patients who have previously participated or are currently participating in any study involving the administration of a CMV vaccine or another CMV investigational agent.

18. Patients who have participated in another interventional clinical study and received another investigational product (ie, not approved by the Food and Drug Administration in the United States or the Ministry of Health, Labour and Welfare in Japan) within 90 days before Randomization.
19. Patients who are unable or unwilling, in the opinion of the Investigator, to comply with the protocol.

STUDY DESIGN AND DURATION:

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).

A schematic representing the study's design is shown below:



*When the patient meets the primary endpoint, the patient move to the rescue phase

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 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 the Early Termination Visit and Withdrawal Procedures.

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 monitoring.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

NPC-21 (at a dose of 6 or 12 mg/kg of actual body weight [at Screening]) or placebo (normal saline) will be administered via an approximately 60-minute (5 mL/minute) intravenous infusion on Day 1 and at Weeks 4, 8, and 12.

EFFICACY VARIABLES:

The primary efficacy endpoint is the incidence 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) by Week 16.

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

IMMUNOGENICITY VARIABLES:

The immunogenicity of NPC-21 in CMV seronegative patients will be evaluated by anti–NPC-21 antibody testing. Blood samples 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 for anti–NPC-21 antibody measurements. Samples may be collected by home healthcare services (United States only) at non-dosing day visits.

VIROLOGY VARIABLES:

Antiviral resistance in CMV seronegative patients will be evaluated by resistant strains genotypic analysis. Blood samples will be stored for screening for resistant strains analysis and will be collected prior to study drug administration on Day 1, at Weeks 16 and 28, and at the initiation of the Rescue Phase. Samples may be collected by home healthcare services (United States only) at non-dosing day visits. The resistant strains analysis of blood samples from patients with treatment failure will be conducted in this Phase 2 study based on analysis study protocol.

SAFETY VARIABLES:

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 adverse event monitoring.

STATISTICAL ANALYSES:

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, the percentage of patients with 95% confidence intervals in each category as descriptive statistics. Statistical tests will be 2-sided at the α=0.05 significance level. The procedures for handling missing, unused, or spurious data,

along with the detailed method for analysis of each variable will be presented in the Statistical Analysis Plan.

Changes in study visit schedules, missed or delayed visits, or patient discontinuations and the relationship to Coronavirus Disease 2019 (COVID-19) will be captured in the electronic Case Report Forms. Protocol deviations in study procedures due to COVID-19 will be reported in the Clinical Study Report.

Analysis Populations

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

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.

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.

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

Analysis of Efficacy

The mITT Population will be used for all efficacy analyses.

The primary efficacy endpoint will be the proportion of patients with 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) by Week 16.

The primary efficacy endpoint will be summarized by treatment group and compared across placebo and the 6 mg/kg NPC-21 treatment group using a logistic regression analysis with stratification factor of region (United States or Japan) as a covariate.

Other efficacy endpoints will be summarized descriptively by treatment group using the mITT Population.

Analysis of Pharmacokinetics

Serum concentrations of NPC-21 will be summarized using descriptive statistics. 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.

Analysis of Exposure-Response

Exposure-response analyses will be performed to propose target concentrations using PK parameters estimated by population-PK, efficacy variables, and biomarkers.

Analysis of Safety

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 adverse events reported during the study.

The number and percentage of patients experiencing treatment-emergent adverse events will be summarized. Summaries will be produced for each body system, as well as for each preferred term using the Medical Dictionary for Regulatory Activities. The number and percentage of patients experiencing serious adverse events will also be summarized.

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 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.

SITES: Approximately 25 clinical sites in the United States and Japan

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
aa	Amino acids
AD	Antigenic domain
ADR	Adverse drug reaction
AESI	Adverse event of special interest
AUC	Area under the concentration-time curve
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
COVID-19	Coronavirus Disease 2019
CRA	Clinical research associate
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EIU	Exposure In Utero
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels questionnaire
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
gB	Glycoprotein B
GCP	Good Clinical Practice
GCV	Ganciclovir
hCMV	Human cytomegalovirus
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVIg	Intravenous immunoglobulin
mITT	Modified Intent-to-Treat

Abbreviation	Definition
NIMP	Non-investigational medicinal product (Note: Except for NPC-21 for this study)
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SAR	Serious adverse reaction
SOT	Solid organ transplant
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
VGCV	Valganciclovir
VZV	Varicella zoster virus
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

Human cytomegalovirus (hCMV) is a member of the *Herpesviridae* family double-stranded deoxyribonucleic acid (DNA) viruses that become latent in host cells after acute infection. Cytomegalovirus (CMV) infection is ubiquitous and high seroprevalence has been reported in worldwide populations. In the United States, CMV seroprevalence ranges from 40% to 80%.[1,2,3] Cytomegalovirus infection is usually harmless, except in the fetus and the immunocompromised host. In the immunocompromised host, primary infection, reinfection, or reactivation of latent virus can cause significant morbidity and mortality. Persons undergoing a solid organ transplant (SOT) are particularly susceptible to both primary infection and reactivation of CMV as a result of the pharmacologic immunosuppression used to prevent graft rejection.

Cytomegalovirus entry into host cells requires the stepwise coordination of multiple virus-encoded envelope proteins. Following viral attachment, which is mediated by interactions between the CMV glycoprotein M/glycoprotein N complex and host heparin sulfate proteoglycans,[4,5] the virus envelope fuses with cellular membranes through the combination of glycoprotein B (gB) and glycoprotein H/glycoprotein L complexes. Glycoprotein B is essential for the attachment, entry, fusion, and cell-to-cell spread of CMV.[5] In addition, gB is the dominant antigen on the CMV envelope, and close to 100% of CMV infected individuals develop antibodies against this glycoprotein.[6] Antibody preadsorption experiments with recombinant-derived gB have shown that in some human sera, a considerable fraction of the neutralizing response is directed against gB.[6,7]

Three antigenic sites, antigenic domain (AD)-1, AD-2, and AD-3, have been identified in gB and consist of amino acids (aa) 552 to 635, aa 50 to 77, and aa 783 to 906, respectively.[8,9,10] Antigenic domain 1 is highly conserved among clinical CMV strains and is an essential structural domain for gB function.[11,12,13] The majority of gB-specific antibodies that develop during natural CMV infection are directed against AD-1,[14] and antibodies that bind to AD-1 can have virus-neutralizing capacity.[15,16] Therefore, AD-1 of CMV gB is a potential candidate region in targeting a neutralizing prophylactic and therapeutic antibody against CMV infection.

Human cytomegalovirus is usually transmitted as an inapparent infection during infancy and establishes a latent infection in T-lymphocytes, monocytes, macrophage cells, or salivary glands. When infected with hCMV for the first time during puberty or later, hCMV infection manifests as infectious mononucleosis-like symptoms, such as fever, swollen lymph nodes, and abnormal hepatic function. However, individuals with reduced immunity, such as those with acquired immunodeficiency, malignant tumors, SOT, and hematopoietic stem cell transplantation (HSCT), develop significant symptoms, such as pneumonia, retinitis, gastroenteritis, and encephalitis, resulting in a poor prognosis.

The morbidity and mortality associated with CMV infection are secondary to both the direct and the indirect effects of CMV. Cytomegalovirus infection can result in CMV disease, both CMV syndrome and CMV tissue-invasive disease. The highest risk of CMV disease occurs in CMV seronegative recipients of an organ from a CMV seropositive donor. Nearly 40,000 SOTs occur in the United States each year.[17] The most common organ transplanted is the kidney, followed by the liver. Because of the immunosuppression required to prevent rejection of the graft, the host is predisposed to infections. Like HSCT recipients, CMV is one of the most important viral infections occurring in SOT. Not only is infection a risk factor for CMV disease, including CMV viral syndrome and tissue-invasive disease, it is also an independent risk factor for secondary bacteremia, Epstein-Barr virus-mediated, post-transplant lymphoproliferative disorder and

allograft injury.[18] Peak viral load, rate of increase of viral load, and a threshold level of viremia have all been associated with risk for CMV disease.[19] Highest risk persons for CMV infection and disease are those that are seronegative recipients paired with a seropositive organ donor. However, seropositive recipients are also at risk for disease.

In SOT recipients, hCMV is a causative virus for morbidity and mortality within 6 months of the transplant.[20,21] In addition, hCMV has been reported to be involved in the risk of developing allograft injury or rejection[22,23] and opportunistic infections.[24] In addition, it has been reported that in transplant recipients not receiving prophylaxis or preemptive treatment, the overall incidence of symptomatic CMV infections reached 40% to 60%, with the incidence and severity being highest among hCMV seronegative recipients transplanted from hCMV seropositive donors.[25] In HSCT recipients, CMV seropositive recipients are at the highest risk for the development of CMV infection regardless of the donor's CMV serostatus. Without intervention, approximately 80% of CMV seropositive HSCT patients will experience CMV infection (viremia) and approximately 30% of patients with CMV viremia will develop CMV disease.[26]

Human cytomegalovirus infection causes organ damage (direct effect) after the stage of hCMV viremia, and affects chronic inflammation and the immune system, leading to acute rejection and the development of new infections (indirect effect). Prevention of hCMV infection is thus critically important for successful organ transplantation. The mainstay in clinical practice is prophylaxis or preemptive treatment with antiviral drugs given transplantation in SOT and HSCT recipients. The first-line antiviral drug used in the treatment is ganciclovir (GCV) or valganciclovir (VGCV). However, the use of GCV, VGCV, and other antiviral drugs raises concerns about serious adverse drug reactions (ADRs), such as bone marrow depression and renal disorder as well as the development of GCV-resistant strains.[27] As an alternative approach, CMV antibodies have been used successfully to treat CMV-induced disease. For example, CMV hyperimmunoglobulin has demonstrated efficacy in certain SOT recipients,[28] and a more recent study found that pooled human immunoglobulin G products from CMV-positive individuals are effective in protecting infants from congenital CMV infection.[29] Likewise, letermovir, a CMV agent intended for prophylaxis, became available recently for use in allogeneic HSCT patients, but its potential risks of drug interaction with immunosuppressive agents and antiviral resistance may limit treatment options.[30] Therefore, the development of a novel drug that provides an effective and safe alternative or addition to current CMV therapies is necessary.

NPC-21 is a human monoclonal immunoglobulin G1 (IgG1) lambda against the AD-1 on hCMV gB. Antigenic domain 1, the dominant antigen of the hCMV envelope, is reported to exhibit little sequence variation in clinical isolates of hCMV.[13] A cell clone that produces NPC-21 was selected from B-lymphocytes isolated from peripheral blood of a healthy individual with a history of CMV infection. NPC-21 is produced by recombinant DNA technology in Chinese hamster ovary cells. NPC-21 has been demonstrated *in vitro* to inhibit infection of a cultivated CMV strain in the pharmacology study using ARPE-19 cell (epidermal cell line).

NPC-21 is a non-immunomodulatory human monoclonal antibody with a relatively safe toxicological profile, causing no deaths and producing only mild reversible changes in hematological parameters (ie, decreased erythrocyte count, hematocrit value, and hemoglobin concentration) following repeated dosing in monkeys. Additionally, no cross reactivity was seen in a study of cross reactivity in human and monkey tissue. Although these changes occurred at a dose with sufficient safety margins and after repeated doses, the hematology parameters will be carefully monitored in clinical studies.

A first-in-human study was conducted in 40 healthy Japanese and Caucasian male volunteers in which NPC-21 or placebo was infused over a duration of 60 minutes. This single ascending dose study confirmed tolerability of NPC-21 up to 20 mg/kg, with no serious adverse events (SAEs), ADRs, or withdrawals due to adverse events. Anti–NPC-21 antibodies were detected in some subjects, although all were found to be preexisting conditions.

Taken together, nonclinical data and clinical data available to date support further clinical investigation of NPC-21 in the prevention of CMV disease.

In March 2020, the Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2, was characterized as a pandemic by the World Health Organization (WHO). The COVID-19 pandemic impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures.

This study protocol includes contingency measures to manage disruptions due to COVID-19; see Section 5.6.2 for information regarding acceptable COVID-19 vaccines and medications and Sections 6, 7.3, 7.4, 8.1, 8.2, 9.7, 9.8, 9.9, 9.10, and 9.12 and Appendix A for details on procedures that may be performed by home healthcare services (United States only) due to COVID-19 restrictions or other concerns, such as the need to avoid risks of COVID-19 infection. The impacts of these implemented contingency measures on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures will be discussed in the Clinical Study Report.

1.1 Rationale

NPC-21 is a fully human monoclonal antibody that targets the AD-1 on hCMV surface gB. Based on binding affinity to the AD-1 and potency of neutralization, a cell clone that expresses NPC-21 was selected from B-lymphocytes isolated from the peripheral blood of a healthy individual with a history of hCMV infection. NPC-21 is composed of two heavy chains (454 amino acid residues) and two light chains (216 amino acid residues) connected by inter-chain disulfide bonds. Chinese hamster ovary cells are used for the production of NPC-21, and the antibody secreted into the growth medium is subsequently purified through a series of filtration and chromatographic steps. The isotype and subclass of NPC-21 were identified as IgG1 lambda. NPC-21 is being developed for the prevention of CMV-associated disease.

Human cytomegalovirus gB is a surface glycoprotein that spans the viral lipid bilayer envelope and is the principle envelope antigen essential for viral attachment, entry, fusion, and cell-to-cell transmission.[5] Close to 100% of individuals who are infected with hCMV develop antibodies against gB.[6] In antibody preadsorption experiments using recombinant-derived gB, results have shown that a considerable fraction of the neutralizing response, in some human sera, was directed against gB.[6,7]

Based on analysis of multiple hCMV clinical isolates, AD-1 is a highly conserved immunogenic, external domain and is an essential structural domain for gB function.[11,12,13] According to Schoppel et al, the majority of gB-specific antibodies that are induced by natural hCMV infection are directed against AD-1,[14] and the antibodies that bind to AD-1 are often neutralizing.[15,16]

NPC-21 acts by binding to AD-1 on the hCMV gB and blocking the essential processes of attachment, entry, fusion, and cell-to-cell spread of hCMV. NPC-21 neutralizes not only the reference laboratory strains AD169,[31] Towne,[32] and Davis,[33] but also the clinical isolate Merlin,[34]

when cultured in human fibroblasts. The 50% inhibitory concentration (IC_{50}) range was 0.015 to 0.032 μg/mL, and the 90% inhibitory concentration (IC_{90}) range was 0.086 to 0.51 μg/mL. Additionally, NPC-21 exhibited 682 to 1977 times more potent neutralization activities when the IC_{90} values for individual strains were compared to those for anti-CMV hyperimmunoglobulin (CytoGam®). Epithelial cells are a principal target for hCMV primary infection, and these cells are highly permissive for replication.[35] Therefore, a strictly cell-associated mode of hCMV infection more accurately reflects the *in vivo* situation.[36] Given this observation, the ability of NPC-21 to inhibit cell-to-cell transmission of epithelial cell-tropic hCMV clinical isolates was examined in human retinal pigment epithelial cells, ie, ARPE-19 cells. NPC-21 inhibited the cell-to-cell transmission of hCMV clinical isolates with an IC_{50} range of 1.0 to 3.1 μg/mL and an IC_{90} range of 13 to 19 μg/mL. In addition, an *in vitro* combination study indicated that the inhibitory effect of NPC-21 on hCMV plaque formation was additive or synergistic with the currently approved viral DNA polymerase inhibitors GCV, cidofovir, foscarnet, and acyclovir, suggesting that NPC-21 does not interfere with DNA polymerase inhibitor antiviral activity and can be potentially used as part of a combination therapy.

Toxicity of NPC-21 was evaluated in compliance with Good Laboratory Practice regulations. Once weekly intravenous administration of NPC-21 in male and female cynomolgus monkeys at doses up to 100 mg/kg for 4 weeks (total of 4 doses) was well-tolerated. There were no deaths, and no adverse clinical signs attributable to NPC-21 treatment were observed in any animal. Treatment with NPC-21 doses of up to 100 mg/kg did not noticeably affect electrocardiography, blood pressure, or respiration rates, suggesting an absence of effects on cardiovascular and respiratory functions. In addition, NPC-21 doses of up to 100 mg/kg had no effects on the central nervous system.

At the 100 mg/kg dose, reversible hematologic changes were observed at the end of the 4-week dosing period (a decreased erythrocyte count, hematocrit value, and hemoglobin concentration in 3 of 12 animals, with an increased reticulocyte ratio in 2 of these animals). The increased or normal reticulocyte ratio and unchanged leukocyte counts in these animals suggested there were minimal toxicological effects on hematopoiesis. The possibility that NPC-21 had some effects on peripheral erythrocytes cannot be excluded. Thus, the no observed adverse effect level was considered to be 50 mg/kg in both male and female monkeys.

A first-in-human Phase 1 study of NPC-21 was conducted in 40 healthy Japanese and Caucasian male adults, in which a single administration of NPC-21 or placebo was infused over a duration of 60 minutes. This single ascending dose study confirmed tolerability of NPC-21 up to 20 mg/kg. All adverse events were mild in severity. There were no SAEs, deaths, significant adverse events, or adverse events that led to treatment discontinuation. Anti–NPC-21 antibodies were detected in 6 out of 40 individuals, but in all cases, the antibodies were present prior to administration of NPC-21.

In the Phase 1 study, the maximum serum concentration, area under the concentration-time curve (AUC) from time 0 to the last measurable concentration, and the AUC from time 0 to infinity increased dose-dependently as was demonstrated by a linear regression analysis and a power model analysis. For other pharmacokinetic parameters (time to maximum serum concentration, half-life [$t_{1/2}$], clearance, volume of distribution, mean residence time, and elimination rate constant), no significant difference between dose levels was observed. The $t_{1/2}$ was estimated to be 612.30 to 790.41 hours, and the elimination pattern was considered biphasic.

Nobelpharma Co., Ltd. proposes to continue the NPC-21 development program with a Phase 2, randomized, double-blind, placebo-controlled study in CMV seronegative patients undergoing a first kidney transplant from a CMV seropositive donor. Eligible patients will be randomized following kidney transplantation and will enter a 16-week Treatment Period, in which they will be randomized to NPC-21 6 mg/kg, NPC-21 12 mg/kg, or placebo on Day 1 and at Weeks 4, 8, and 12 for 16 weeks (total of 4 infusions). Safety will be closely monitored throughout the duration of the study. At any time during the study, patients who develop detectable CMV viremia or CMV disease can enter the Rescue Phase of the study and be treated by standard preemptive CMV therapy.

1.2 Risk/Benefit

Cytomegalovirus disease causes significant morbidity and mortality in transplant recipients. Prevention or treatment with directed antivirals or immunoglobulins is associated with toxicity and high cost, and does not eliminate all of the associated morbidities. The expected advantage of NPC-21, a human monoclonal antibody against the AD-1 on CMV gB, is superior safety profiles. NPC-21 binds to AD-1 specific on CMV gB to inhibit the cell-to-cell transmission of hCMV.

Phase 1 study data indicate NPC-21 has been generally safe and well tolerated, although the number of subjects studied to date is relatively small. A total of 40 subjects (32 Japanese, 8 Caucasian) were enrolled in the Phase 1 study. The study incorporated a total of 5 steps, consisting of 4 dose groups of 1, 3, 10, and 20 mg/kg for Japanese subjects, and 1 dose group of 10 mg/kg for Caucasian subjects. Overall, NPC-21 was safe and well tolerated. There were no deaths or SAEs. A total of 23 adverse events in 16 subjects were all mild in severity and not related to the study drug. In addition, there were no adverse events leading to discontinuation or other significant adverse events. No particular correlation was found between the dose level of the test drug and the incidence of adverse events. When Japanese and Caucasian subjects were compared at the same dose level (10 mg/kg), the nature and pattern of adverse events were comparable, showing no obvious difference between the 2 races. Laboratory related adverse events were also reported but all were mild in severity and judged not related to the study drug. Anti–NPC-21 antibody was detected in 6 subjects, but 1 subject was from the placebo group and, in all cases, the antibodies were present prior to administration of NPC-21. There was no tendency toward increase in antibody concentration after the study treatment.

In the Phase 1 single dose study, no conditions suggestive of anaphylaxis associated with NPC-21 were observed. Serious hypersensitivity reactions, such as anaphylaxis, have been reported with the use of other antibody drugs. Therefore, the possibility of such reactions to NPC-21, an antibody drug, cannot be ruled out.

2 STUDY OBJECTIVE

2.1 Primary Objective

The primary objective is to assess the efficacy and safety of NPC-21 when administered prophylactically to CMV seronegative patients receiving a first kidney transplant from a CMV seropositive donor.

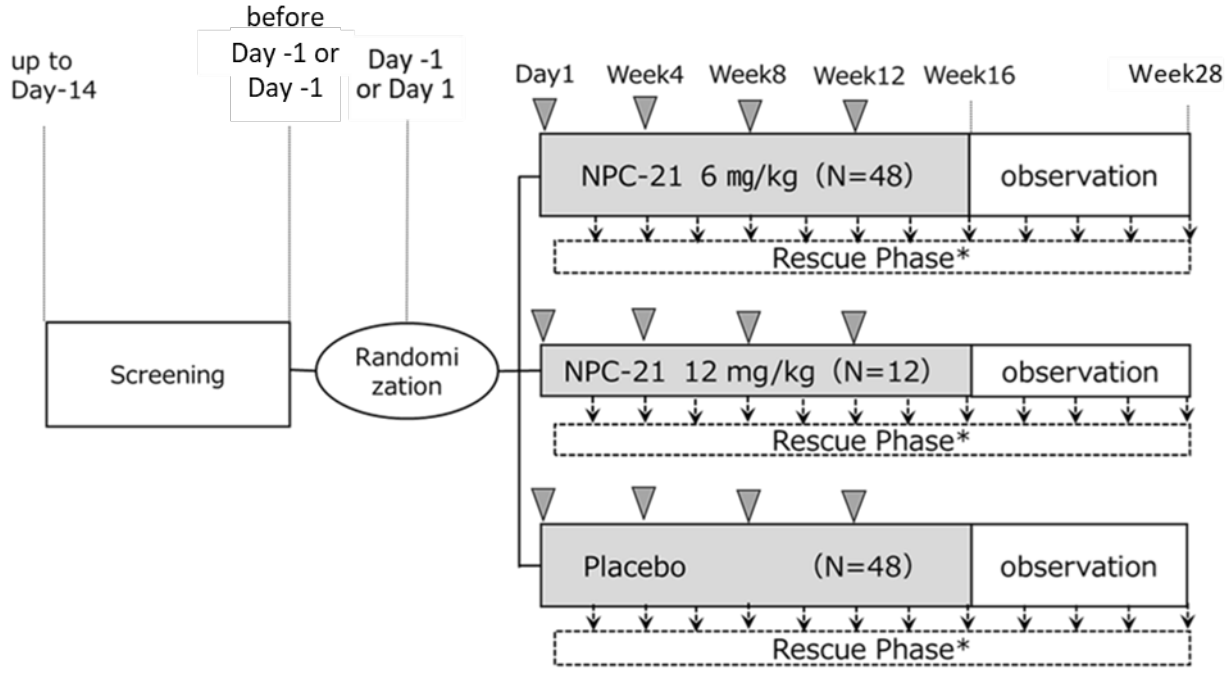
3 STUDY DESCRIPTION

3.1 Summary of Study Design

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



*When the patient meets the primary endpoint, the patient move to the rescue phase

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 Early Termination Visit and Withdrawal Procedures.

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 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 monitoring.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients 18 to ≤75 (<76) years of age in the United States or 20 to ≤75 (<76) years of age in Japan at the time of obtaining informed consent.
2. Patients must be CMV seronegative pre-transplant and scheduled to receive or have received (within 7 days prior to first study drug administration) a first kidney transplant from a CMV seropositive donor.
3. Patients must be willing and able to give written informed consent for participation in the study.
4. Patients must be eligible to undergo kidney transplantation from a living or deceased donor, as per institutional standards.
5. Female patients of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before Screening) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone (FSH) in the postmenopausal range at Screening, based on the laboratory's reference range.
6. Female patients of childbearing potential (ie, not postmenopausal or surgically sterilized) must have a negative urine or serum pregnancy test result at Screening. Participating female patients of childbearing potential must agree to use 1 of the following throughout the duration of the study and for 90 days following the last study drug administration:
   - One highly effective method of contraception and an acceptable barrier method (condom used by male partner plus spermicide).
   - Two highly effective methods of contraception.

   Investigators will select the appropriate methods of contraception in accordance with local regulatory requirements. Highly effective methods of contraception that result in a low failure rate (ie, <1% per year) when used consistently and correctly include the following:
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, or intrauterine hormone-releasing system for at least 12 weeks before Screening.
   - Bilateral tubal occlusion or vasectomized partner at least 26 weeks before Screening.

     Note: A vasectomized partner is a highly effective method of contraception, provided that the male partner is the sole sexual partner of the study patient who is a female of childbearing potential and that the vasectomized partner has received medical assessment of surgical success.

- Sexual abstinence.

  Note: True abstinence, when in line with the preferred and usual lifestyle of the patient, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

7. Male patients must agree to abstain from sperm donation and use condoms with spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug. Male patients must ensure nonpregnant female partners of childbearing potential comply with the contraception requirements in Inclusion Criterion 6.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Patients who have received a previous solid organ transplantation or HSCT.
2. Patients who receive a multi-organ transplant.
3. Patients who have CMV disease (CMV syndrome or tissue-invasive CMV disease) or CMV viremia (PCR analysis or antigenemia testing in local laboratory meets the local criteria for CMV viremia) at Screening.
4. Patients who have a positive donor-specific antibody within 90 days prior to Randomization confirmed via medical records.
5. Patients whose body weight is more than 120 kg at Screening.

   Note: In case of hemodialysis patients, body weight is defined immediately after dialysis or dry weight. In case of peritoneal dialysis patients, body weight is defined after removal of dialysate or dry weight.

   Note: Body weight measured within 7 days prior to pre-Randomization is permitted.

6. Patients who have received the following anti-CMV therapy within 7 days prior to Randomization and/or plan to receive the following anti-CMV therapy during the study:

   - Anti-CMV agents (eg, foscarnet, GCV, VGCV, letermovir, high dose acyclovir [≥500 mg/m^2 intravenously every 8 hours, 10 mg/kg intravenously every 8 hours or 800 mg orally 4 times a day], high dose valacyclovir [1000 mg orally 3 times a day], high dose famciclovir [500 mg orally every 8 hours], or cidofovir).

     Note: The use of anti-CMV agents per local standard of care during the Rescue Phase of the study is permitted.

     Note: The use of anti-herpes simplex virus (HSV) and anti-varicella zoster virus (VZV) prophylaxis for at-risk patients is recommended (as long as the doses are below the one specified above).

7. Patients who have received the following therapy within 28 days prior to Randomization and/or plan to receive the following anti-CMV therapy during the study:
   - CMV hyperimmune globulin (eg, CytoGam®).
   - Intravenous immunoglobulin (IVIg).
   - Plasmapheresis (receipt prior to first study drug administration is acceptable).
8. Patients with a history of a serious drug allergy to proteins, immunoglobulins, transfusions, or vaccines or any excipient of the NPC-21 formulation.
9. Patients with severe hepatic insufficiency at Screening (eg, Child-Pugh Class C).
10. Patients with active and untreated hepatitis B virus or hepatitis C virus, as documented as part of the pre-transplant testing.
11. Patients with known human immunodeficiency virus infection, based on medical records serology.
12. Patients with any uncontrolled infection at Randomization or a history of serious and uncontrolled infection within 6 months prior to Randomization.
13. Patients who are pregnant or lactating.
14. Patients with a history of malignancy within 5 years prior to Randomization other than curatively treated in situ cervical carcinoma, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
15. Patients with a history of alcohol or drug abuse or dependence within 1 year prior to Randomization that, in the opinion of the Investigator, would preclude study participation.
16. Patients who have previously participated in this study or any other study involving NPC-21.
17. Patients who have previously participated or are currently participating in any study involving the administration of a CMV vaccine or another CMV investigational agent.
18. Patients who have participated in another interventional clinical study and received another investigational product (ie, not approved by the Food and Drug Administration [FDA] in the United States or the Ministry of Health, Labour and Welfare in Japan) within 90 days before Randomization.
19. Patients who are unable or unwilling, in the opinion of the Investigator, to comply with the protocol.

4.3 Withdrawal Criteria

Patients may be discontinued from study drug for any of the following reasons:

- The patient no longer meets all inclusion criteria or meets any exclusion criteria and is found to be ineligible for participation through procedures (eg, medical examinations) performed after Randomization.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.

- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
- Pregnancy.
- Requirement of the following therapy:
  - CMV hyperimmune globulin (eg, CytoGam®).
  - IVIg.
  - Plasmapheresis.
- Patient failure to comply with protocol requirements or study-related procedures and the Investigator considers it inappropriate to administer the study drug.
- Initiation of Rescue Phase.

Patients who discontinue study drug for any reason should be followed per the study schedule of events until the end of study participation.

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason.
- Termination of the study by the Sponsor or the regulatory authority.
- If a patient develops COVID-19 and is unable to continue with study visits and observations, the patient should be discontinued from the study and standard of care CMV treatment should be initiated, if necessary. If COVID-19 treatment will be provided to the patient, the Investigator should notify the Medical Monitor prior to study discontinuation, if possible. All patients should be followed for safety and resolution of COVID-19 infection. Patients who are able to complete study-related visits as an outpatient or via home healthcare services (United States only) or are inpatient and can receive study treatment will be allowed to continue to participate in the study if they do not receive any experimental treatments for COVID-19.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the End of Treatment visit (Week 28). The reason for patient withdrawal must be documented in the electronic Case Report Form (eCRF).

Withdrawn patients will not be replaced.

The Sponsor may consider immediately stopping or terminating the study for any of the following reasons:

- Data and Safety Monitoring Board (DSMB) recommendation.
- Grade 3 or higher infusion reactions are observed in >3 patients.

- Decision from a competent authority.
- Lack of study drug supply.

5 STUDY TREATMENTS

5.1 Treatment Groups

Eligible patients will be randomized in a 4:1:4 ratio prior to first study drug administration to 1 of the following treatment groups:

- NPC-21 (at a dose of 6 mg/kg of actual body weight [at Screening]) administered via an approximately 60-minute (5 mL/minute) intravenous infusion
- NPC-21 (at a dose of 12 mg/kg of actual body weight [at Screening]) administered via an approximately 60-minute (5 mL/minute) intravenous infusion
- Placebo (normal saline) administered via an approximately 60-minute (5 mL/minute) intravenous infusion

5.2 Rationale for Dosing

NPC-21 at a dose of 6 or 12 mg/kg of actual body weight (at Screening) will be administered via an approximately 60-minute (5 mL/minute) intravenous infusion. These doses were determined based on the pharmacokinetic (PK) and safety and tolerability data up to 20 mg/kg from the Phase 1 single dose clinical study.

From the inhibitory effect of NPC-21 on the cell-to-cell transmission of 8 hCMV clinical isolates, NPC-21 inhibited cell-to-cell transmission of all clinical hCMV isolates tested with IC_{90} range of 13 to 19 μg/mL. The Sponsor concludes that NPC-21 is effective in the prevention of CMV infection when the trough concentration of NPC-21 is over 19 μg/mL. Based on simulations using the PK data from the Phase 1 study, it is assumed that 6 mg/kg once every 4 weeks will keep 19 μg/mL at the lower limit of the 95% confidence interval at the trough of Day 29. A small cohort of 12 mg/kg NPC-21 has been added for exposure-response analysis.

5.3 Randomization and Blinding

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.

The Sponsor designee (eg, IRT vendor) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind integrity is properly maintained. Care should be exercised to ensure that only study staff

or Sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in SAE reporting, dispensing pharmacist). Randomization information will be concealed from the Investigators and the patients until the end of the study, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment.

5.4 Breaking the Blind

Unblinding should only occur in the event of an emergency or adverse event for which it is necessary to know study drug treatment to determine the appropriate course of therapy. If the patient's study drug must be unblinded, the Investigator or qualified designee should contact IRT, but not the site's unblinded pharmacist, for study drug information. The IRT documentation indicating the blind break at the site must be retained with the patient's source documentation in such a way as to avoid unblinding the treatment assignment to other site or the Sponsor blinded personnel.

If possible, the Investigator should attempt to contact the Medical Monitor prior to unblinding. If not possible, the Investigator should notify the Medical Monitor within 24 hours of the unblinding without disclosing the treatment assignment of the unblinded patient. The Investigator must document the patient's identification, the reason for breaking the blind, and the date and time for breaking the blind, but not the treatment assignment.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

[redacted]

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

Study drug will have a label indicating the lot number, storage conditions, and the Sponsor identification, as well as appropriate cautionary language for investigative material.

Study drug will be packaged according to current Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines and labeled according to the requirements of local law and legislation. Proof labels, detailing actual label text, will be available in the study files.

5.5.2 Study Drug Preparation and Dispensing

Prior to administration, based on a dose of 6 or 12 mg/kg of actual body weight (at Screening), the required NPC-21 will be diluted with sterile saline into an intravenous infusion bag according to the Pharmacy Manual to make a total volume of approximately 300 mL.

Note: In case of hemodialysis patients, body weight is defined immediately after dialysis or dry weight. In case of peritoneal dialysis patients, body weight is defined after removal of dialysate or dry weight.

Additional details regarding study drug preparation and dispensing are provided in the Pharmacy Manual.

5.5.3 Study Drug Administration

Patients randomized to NPC-21 will be administered a dose of 6 or 12 mg/kg of actual body weight (at Screening) via an approximately 60-minute (5 mL/minute) intravenous infusion on Day 1 and at Weeks 4, 8, and 12.

Patients randomized to placebo will be administered approximately 300 mL of normal saline via an approximately 60-minute (5 mL/minute) intravenous infusion on Day 1 and at Weeks 4, 8, and 12.

Patients will be asked to remain at rest in the supine position, in principle, during study drug administration and should remain resting, in principle, from the end of study drug administration until the tests scheduled within 1 hour after study drug administration.

If an adverse event, especially an infusion reaction, occurs during study drug administration and the Investigator deems it necessary, deceleration, suspension, or resumption of study drug administration is allowed. In case of a Grade 2 infusion reaction, study drug administration will be suspended and study drug administration will be resumed (flow rate will be 2.5 mL/minute) after recovery from the symptoms by treatments. In the case of a Grade 3 or higher infusion reaction, study drug administration will be terminated. Details will be entered in the eCRF. Refer to the Pharmacy Manual for more information.

The day of administration as well as the administration start and end time will be entered in the eCRF.

5.5.4 Treatment Compliance

Study drug will be administered intravenously by site staff. Dosing compliance will be recorded by the Investigator or designee at the site. The date and time of study drug administration will be recorded.

5.5.5 Storage and Accountability

Records will be maintained indicating the receipt and dispensation of all study drug supplies. At the conclusion of the study, the clinical research associate (CRA) will conduct an unblinded review of study drug inventory, and the results will be recorded in the Drug Accountability Log. Any unused drug will be returned to the depot. If no study drug remains, this will be indicated in the Drug Accountability Log.

Study drug will be stored at [redacted] in a secured area with access limited to authorized personnel. The unblinded site pharmacist will perform an ongoing inventory of study drug products on behalf of the Sponsor and must keep an accurate inventory of study drug shipments received and amount of study drug used per patient.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The following anti-CMV therapies will be prohibited within 7 days prior to Randomization through the end of the study:

- Anti-CMV agents (eg, foscarnet, GCV, VGCV, letermovir, high dose acyclovir [≥500 mg/m^2 intravenously every 8 hours, 10 mg/kg intravenously every 8 hours or 800 mg orally 4 times a day], high dose valacyclovir [1000 mg orally 3 times a day], high dose famciclovir [500 mg orally every 8 hours], or cidofovir).

  Note: The use of anti-CMV agents per local standard of care during the Rescue Phase of the study is permitted.

  Note: The use of anti-HSV and anti-VZV prophylaxis for at-risk patients is recommended (as long as the doses are below the one specified above).

The following therapies will be prohibited within 28 days prior to Randomization through the end of the study:

- CMV hyperimmune globulin (eg, CytoGam®)
- IVIg
- Plasmapheresis (receipt prior to first study drug administration is acceptable)

5.6.2 Coronavirus Disease 2019 Vaccination, Treatment, and Care

The following COVID-19 vaccines and medications are acceptable:

- It is acceptable for patients to receive COVID-19 vaccinations where emergency use authorization is given. COVID-19 vaccinations given to prevent COVID-19 infections must not be administered within 72 hours of the study drug administration.
- Medications that are approved by regulatory authorities for other indications (eg, dexamethasone) may be given for COVID-19 infections while the patient is in the study. Experimental medications for COVID-19 infections will be excluded (eg, mesenchymal stem cells).

5.6.3 Documentation of Prior and Concomitant Medication Use

All medications (including COVID-19 vaccinations) taken by the patient within 14 days prior to study drug administration on Day 1 will be recorded (COVID-19 vaccinations administered prior to informed consent will also be recorded). During the study, any medications (including COVID-19 vaccinations or medications) administered in addition to study drug, whether allowed per the protocol or not, must be documented in the eCRF. The drug name, start and end date(s), and indication will be recorded for all medications. Dosing information will also be recorded for immunosuppression therapy, induction therapy, and anti-CMV agents.

6 STUDY PROCEDURES

Adult CMV seronegative patients must be scheduled to receive or have received (within 7 days prior to first study drug administration) a first kidney transplant from a CMV seropositive donor. The 16-week Treatment Period will begin as soon as practical post-transplant but no later than 7 days post-transplant.

During the Treatment Period, visits on dosing days (Day 1 and at Weeks 4, 8, and 12) should be conducted in person.

Home healthcare services (United States only) may be utilized for non-dosing day visits of the Treatment Period and Observation Period, as shown in Figure 2, and at Rescue Phase visits due to COVID-19 restrictions or other concerns, such as the need to avoid risks of COVID-19 infection.

Home healthcare services may perform the following procedures at non-dosing day visits: record concomitant medications, obtain body weight, perform physical examination, record vital signs, collect samples for analysis by the central laboratory, perform 12-lead ECG, perform EQ-5D-5L, and record adverse events. See the study reference manual for details.

Figure 2. Home Healthcare Services

	Treatment Period																	Observation Period					
Study Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17 18 19	20	21 22 23	24	26	28 ET
HH Eligible		X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X

ET = Early Termination; HH = home healthcare.

6.1 Informed Consent

Written informed consent for the study will be obtained from all patients before any study-specific procedures are performed. See Section 12.3 for details on informed consent.

6.2 Screening Visit (Day -14 to Day -1)

The following procedures will be performed at the Screening Visit:

- Obtain informed consent.
- Perform pre-Randomization (see Section 6.3 for details).
- Obtain demographics.
- Obtain medical/surgical history and present illness.
- Record prior and concomitant medications.
- Obtain height.
- Obtain body weight (prior to pre-Randomization).

  Note: In case of hemodialysis patients, body weight is defined immediately after dialysis or dry weight. In case of peritoneal dialysis patients, body weight is defined after removal of dialysate or dry weight.

Note: Body weight measured within 7 days prior to pre-Randomization is permitted.

- Perform complete physical examination.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Perform urine or serum pregnancy test for females of childbearing potential only.
- Perform FSH test for females of non-childbearing potential only (if necessary).
- Collect blood sample for CMV serology for analysis by the local laboratory (within 90 days of Randomization).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory.
- Collect urine sample for urinalysis by the local laboratory (if possible).
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Perform 12-lead ECG.
- Confirm patient meets all inclusion criteria and no exclusion criteria (until Randomization).
- Perform Randomization if Randomization will occur on Day -1 (see Section 6.3 for details).
- Record adverse events.

6.3 Pre-Randomization and Randomization

6.3.1 Pre-Randomization

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).

6.3.2 Randomization

Randomization will take place prior to the first study drug administration after confirming all criteria. Randomization procedures may occur on Day -1 or Day 1 prior to first study drug administration. If the patient is found to be ineligible during Screening, the dropout procedures will be carried out promptly.

6.4 Treatment Period (Day 1 to Day 113)

The 16-week Treatment Period will begin as soon as practical post-transplant but no later than 7 days post-transplant. During the Treatment Period (excluding Day 1), visits and procedures will occur within ±3 days of the scheduled time. After first study drug administration, patients who develop detectable CMV disease (CMV syndrome [see Appendix C for definition of CMV syndrome] or tissue-invasive CMV disease [see Appendix D 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) 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 Early Termination Visit and Withdrawal Procedures. See Section 6.6 for a list of procedures to be performed upon entering the Rescue Phase.

Note: During the Treatment Period, visits on dosing days (Day 1 and at Weeks 4, 8, and 12) should be conducted in person. Visits on non-dosing days of the Treatment Period (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, and 16) may be conducted by home healthcare services (United States only).

6.4.1 Day 1

The following procedures will be performed at Day 1:

- Record prior and concomitant medications.
- Obtain body weight (prior to study drug administration).
- Perform complete physical examination (prior to study drug administration and within 1 hour of the end of the infusion).
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) (prior to study drug administration and within 1 hour of the end of the infusion).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory (prior to study drug administration).
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory (prior to study drug administration).
- Collect blood samples that will be stored for screening for resistant strains analysis (prior to study drug administration).
- Collect blood sample for serum NPC-21 concentration measurement (within 2 hours prior to study drug administration and at 2 hours [±30 minutes] following the beginning of the infusion).
- Collect blood sample for anti–NPC-21 antibody measurement (prior to study drug administration).
- Perform EQ-5D-5L (prior to study drug administration).
- Perform Randomization (prior to study drug administration) if Randomization will occur on Day 1 (see Section 6.3 for details).
- Administer NPC-21 (at a dose of 6 or 12 mg/kg of actual body weight [at Screening]) or placebo via an approximately 60-minute intravenous infusion at a constant rate of 5 mL/minute.

Note: Patients will be asked to remain at rest in the supine position, in principle, during study drug administration and should remain resting, in principle, from the end of study drug administration until the tests scheduled within 1 hour after study drug administration.

Note: If an adverse event occurs during study drug administration and the Investigator deems it necessary, deceleration, suspension, or resumption of study drug administration is allowed (see Section 5.5.3 for details).

- Record adverse events.

6.4.2 Weeks 1, 2, and 3 (Days 8, 15, and 22)

The following procedures will be performed at Weeks 1, 2, and 3 (Days 8, 15, and 22):

- Record concomitant medications.
- Perform complete physical examination.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (Weeks 1 and 2 only).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (Weeks 1 and 2 only) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement.
- Record adverse events.

6.4.3 Week 4 (Day 29)

The following procedures will be performed at Week 4 (Day 29):

- Record concomitant medications.
- Obtain body weight (prior to study drug administration).
- Perform complete physical examination (prior to study drug administration).
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) (prior to study drug administration).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory (prior to study drug administration).

- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory (prior to study drug administration).
- Collect blood sample for serum NPC-21 concentration measurement (within 2 hours prior to study drug administration and at 2 hours [±30 minutes] following the beginning of the infusion).
- Collect blood sample for anti–NPC-21 antibody measurement (prior to study drug administration).
- Perform 12-lead ECG (prior to study drug administration).
- Administer NPC-21 (at a dose of 6 or 12 mg/kg of actual body weight [at Screening]) or placebo via an approximately 60-minute intravenous infusion at a constant rate of 5 mL/minute.

  Note: Patients will be asked to remain at rest in the supine position, in principle, during study drug administration and should remain resting, in principle, from the end of study drug administration until the tests scheduled within 1 hour after study drug administration.

  Note: If an adverse event occurs during study drug administration and the Investigator deems it necessary, deceleration, suspension, or resumption of study drug administration is allowed (see Section 5.5.3 for details).
- Record adverse events.

6.4.4 Weeks 5, 6, and 7 (Days 36, 43, and 50)

The following procedures will be performed at Weeks 5, 6, and 7 (Days 36, 43, and 50):

- Record concomitant medications.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (Week 6 only).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (Week 6 only) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement (Week 6 only).
- Record adverse events.

6.4.5 Week 8 (Day 57)

The following procedures will be performed at Week 8 (Day 57):

- Record concomitant medications.
- Obtain body weight (prior to study drug administration).

- Perform complete physical examination (prior to study drug administration).
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) (prior to study drug administration).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory (prior to study drug administration).
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory (prior to study drug administration).
- Collect blood sample for serum NPC-21 concentration measurement (within 2 hours prior to study drug administration and at 2 hours [±30 minutes] following the beginning of the infusion).
- Collect blood sample for anti–NPC-21 antibody measurement (prior to study drug administration).
- Perform 12-lead ECG (prior to study drug administration).
- Administer NPC-21 (at a dose of 6 or 12 mg/kg of actual body weight [at Screening]) or placebo via an approximately 60-minute intravenous infusion at a constant rate of 5 mL/minute.

  Note: Patients will be asked to remain at rest in the supine position, in principle, during study drug administration and should remain resting, in principle, from the end of study drug administration until the tests scheduled within 1 hour after study drug administration.

  Note: If an adverse event occurs during study drug administration and the Investigator deems it necessary, deceleration, suspension, or resumption of study drug administration is allowed (see Section 5.5.3 for details).
- Record adverse events.

6.4.6 Weeks 9, 10, and 11 (Days 64, 71, and 78)

The following procedures will be performed at Weeks 9, 10, and 11 (Days 64, 71, and 78):

- Record concomitant medications.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (Week 10 only).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (Week 10 only) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.

- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement (Week 10 only).
- Record adverse events.

6.4.7 Week 12 (Day 85)

The following procedures will be performed at Week 12 (Day 85):

- Record concomitant medications.
- Obtain body weight (prior to study drug administration).
- Perform complete physical examination (prior to study drug administration).
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) (prior to study drug administration).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (prior to study drug administration) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory (prior to study drug administration).
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory (prior to study drug administration).
- Collect blood sample for serum NPC-21 concentration measurement (within 2 hours prior to study drug administration and at 2 hours [±30 minutes] following the beginning of the infusion).
- Collect blood sample for anti–NPC-21 antibody measurement (prior to study drug administration).
- Perform 12-lead ECG (prior to study drug administration).
- Administer NPC-21 (at a dose of 6 or 12 mg/kg of actual body weight [at Screening]) or placebo via an approximately 60-minute intravenous infusion at a constant rate of 5 mL/minute.

  Note: Patients will be asked to remain at rest in the supine position, in principle, during study drug administration and should remain resting, in principle, from the end of study drug administration until the tests scheduled within 1 hour after study drug administration.

  Note: If an adverse event occurs during study drug administration and the Investigator deems it necessary, deceleration, suspension, or resumption of study drug administration is allowed (see Section 5.5.3 for details).
- Record adverse events.

6.4.8 Weeks 13, 14, and 15 (Days 92, 99, and 106)

The following procedures will be performed at Weeks 13, 14, and 15 (Days 92, 99, and 106):

- Record concomitant medications.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites) (Week 14 only).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (Week 14 only) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement (Week 14 only).
- Record adverse events.

6.4.9 Week 16 (Day 113)

The following procedures will be performed at Week 16 (Day 113):

- Record concomitant medications.
- Obtain body weight.
- Perform complete physical examination.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement.
- Collect blood sample for anti–NPC-21 antibody measurement.
- Collect blood samples that will be stored for screening for resistant strains analysis.
- Perform 12-lead ECG.
- Perform EQ-5D-5L.
- Record adverse events.

6.5 Observation Period (Day 114 to Day 197)

During the 12-week Observation Period, visits and procedures will occur within ±3 days of the scheduled time. After first study drug administration, patients who develop detectable CMV disease (CMV syndrome [see Appendix C for definition of CMV syndrome] or tissue-invasive CMV disease [see Appendix D 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) 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 Early Termination Visit and Withdrawal Procedures. See Section 6.6 for a list of procedures to be performed upon entering the Rescue Phase.

Note: Home healthcare services (United States only) may be utilized at Weeks 17, 18, 19, 20, 21, 22, 23, 24, 26, and 28.

Note: During the 12-week Observation Period, visits at Weeks 17, 19, 21, and 23 may be missed due to unavoidable circumstances (eg, holidays, natural disasters). However, every attempt should be made to ensure a visit occurs. In this case, study staff will make contact with the patient to evaluate their condition, eg, review concomitant medications, any new adverse events since the last visit.

6.5.1 Weeks 17, 18, and 19 (Days 120, 127, and 134)

The following procedures will be performed at Weeks 17, 18, and 19 (Days 120, 127, and 134):

Note: During the 12-week Observation Period, visits at Weeks 17 and 19 may be missed due to unavoidable circumstances (eg, holidays, natural disasters). However, every attempt should be made to ensure a visit occurs. In this case, study staff will make contact with the patient to evaluate their condition, eg, review concomitant medications, any new adverse events since the last visit.

- Record concomitant medications.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.

  Note: It is not necessary to collect blood samples for the local laboratory in the case home healthcare services (United States only) are utilized.
- Record adverse events.

6.5.2 Week 20 (Day 141)

The following procedures will be performed at Week 20 (Day 141):

- Record concomitant medications.
- Obtain body weight.

- Perform complete physical examination.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement.
- Perform 12-lead ECG.
- Record adverse events.

6.5.3 Weeks 21, 22, and 23 (Days 148, 155, and 162)

The following procedures will be performed at Weeks 21, 22, and 23 (Days 148, 155, and 162):

Note: During the 12-week Observation Period, visits at Weeks 21 and 23 may be missed due to unavoidable circumstances (eg, holidays, natural disasters). However, every attempt should be made to ensure a visit occurs. In this case, study staff will make contact with the patient to evaluate their condition, eg, review concomitant medications, any new adverse events since the last visit.

- Record concomitant medications.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.

  Note: It is not necessary to collect blood samples for the local laboratory in the case home healthcare services (United States only) are utilized.
- Record adverse events.

6.5.4 Week 24 (Day 169)

The following procedures will be performed at Week 24 (Day 169):

- Record concomitant medications.
- Obtain body weight.
- Perform complete physical examination.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites).

- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement.
- Perform 12-lead ECG.
- Record adverse events.

6.5.5 Week 26 (Day 183)

The following procedures will be performed at Week 26 (Day 183):

- Record concomitant medications.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.

  Note: It is not necessary to collect blood samples for the local laboratory in the case home healthcare services (United States only) are utilized.
- Record adverse events.

6.5.6 Week 28 (Day 197)

The following procedures will be performed at Week 28 (Day 197):

- Record concomitant medications.
- Obtain body weight.
- Perform complete physical examination.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Perform urine or serum pregnancy test for females of childbearing potential only.
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement.

- Collect blood sample for anti–NPC-21 antibody measurement.
- Collect blood samples that will be stored for screening for resistant strains analysis.
- Perform 12-lead ECG.
- Perform EQ-5D-5L.
- Record adverse events.

6.6 Rescue Phase

After first study drug administration, patients who develop detectable CMV disease (CMV syndrome [see Appendix C for definition of CMV syndrome] or tissue-invasive CMV disease [see Appendix D 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) 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 Early Termination Visit and Withdrawal Procedures.

Note: Collection of blood samples for serum NPC-21 concentration measurement at Weeks 4, 8, and 12 during the Rescue Phase will be handled in the same manner as visits without study drug administration.

Note: If the patient is negative for CMV viremia or has recovered from CMV disease before 4 Study Weeks have passed following last study drug administration, weekly scheduled visits are not required. The Rescue Phase visits may be conducted by home healthcare services (United States only). The Rescue Phase procedures may be performed at the next scheduled visit after detecting CMV viremia or CMV disease with or without anti-CMV agents per local standard of care. Some Investigators may prescribe anti-CMV agents (eg, VGCV) in advance and instruct the patient to start taking the drug as soon as possible for safety if the disease or viremia develops. If this is the case, the Rescue Phase procedures may be performed at the next scheduled visit.

The following procedures will be performed upon entering the Rescue Phase:

- Record the rescue in IRT.
- Record concomitant medications.
- Record the date and reason for entering the Rescue Phase.
- Perform complete physical examination.
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples that will be stored for screening for resistant strains analysis.
- Perform EQ-5D-5L.
- Record adverse events.

6.7 Early Termination Visit and Withdrawal Procedures

The end of treatment for patients completing the study is Week 28. For patients who are withdrawn from the study prior to completion, all Week 28 procedures will be performed at an Early Termination visit. The Early Termination visit may be conducted by home healthcare services (United States only). These procedures include the following:

- Record concomitant medications.
- Obtain body weight.
- Perform complete physical examination.
- Record vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature).
- Perform urine or serum pregnancy test for females of childbearing potential only.
- Collect blood samples for blood biochemistry, hematology, and coagulation for analysis by the local laboratory (Japan sites) and central laboratory (US sites).
- Collect urine sample for urinalysis by the local laboratory (Japan sites) and central laboratory (US sites) (if possible).
- Collect blood sample for CMV DNA analysis by the central laboratory.
- Collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
- Collect blood sample for serum NPC-21 concentration measurement.
- Collect blood sample for anti–NPC-21 antibody measurement.
- Collect blood samples that will be stored for screening for resistant strains analysis.
- Perform 12-lead ECG.
- Perform EQ-5D-5L.
- Record adverse events.

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the incidence of CMV disease (CMV syndrome [see Appendix C for definition of CMV syndrome] or tissue-invasive CMV disease [see Appendix D 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.

7.2 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

7.3 Cytomegalovirus Deoxyribonucleic Acid and Antigenemia Test

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 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. Samples for evaluation by the central laboratory may be collected by home healthcare services (United States only) at non-dosing day visits.

Home healthcare services (United States only) may be utilized for CMV PCR analysis at the central laboratory. In the case home healthcare services (United States only) are utilized, it is not necessary to collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory. See the study reference manual for details.

7.4 EuroQol 5 Dimensions 5 Levels Questionnaire

The EQ-5D-5L (paper version) 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 EQ-5D-5L may be performed by home healthcare services (United States only) at non-dosing day visits.

8 IMMUNOGENICITY AND VIROLOGY ASSESSMENTS

8.1 Anti–NPC-21 Antibody

The immunogenicity of NPC-21 in CMV seronegative patients will be evaluated by anti–NPC-21 antibody testing. Blood will be drawn prior to study drug administration on dosing days (Day 1 and at Weeks 4, 8, and 12) and at Weeks 16 and 28 for anti–NPC-21 antibody measurements. Samples may be collected by home healthcare services (United States only) at non-dosing day visits.

8.2 Screening for Resistant Strains Analysis

Antiviral resistance in CMV seronegative patients will be evaluated by resistant strains genotypic analysis. Blood samples will be stored for screening for resistant strains analysis and will be collected prior to study drug administration on Day 1, at Weeks 16 and 28, and at the initiation of the Rescue Phase. Samples may be collected by home healthcare services (United States only) at non-dosing day visits. The resistant strains analysis of blood samples from patients with treatment failure will be conducted in this Phase 2 study based on analysis study protocol.

9 SAFETY ASSESSMENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time informed consent is obtained until Week 28. Should the patient terminate the study early, SAEs should be reported up until the Early Termination visit or 90 days after the last administration of study drug, whichever is later. Patients should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at the time informed consent is obtained, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at the time of signing informed consent should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at Baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Laboratory Abnormalities

Clinically significant abnormal laboratory or other examination (eg, ECG, CMV testing) findings that are detected during the study or are present at the time informed consent is obtained and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

Where possible, the specific disease or syndrome that caused the abnormal laboratory result should be recorded as the adverse event term.

9.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

9.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For NPC-21 the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report. Any adverse event that is both unexpected (not consistent with the applicable product information) and also meets the definition of an SAE/serious adverse reaction (SAR) would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, severe, life-threatening, or death and will also categorize each adverse event as to its potential relationship to study drug using the categories of related or not related.

Assessment of Severity

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For those adverse event terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death related to the adverse event

Causality Assessment

The relationship of an adverse event to the administration of study drug is to be assessed according to the following definitions:

Not related (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a

causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Related (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after study drug is given. The length of time from study drug exposure to the event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant medication-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- The known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology of study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of study drug should be considered.

9.1.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for predefined adverse events of special interest (AESIs) throughout the patient's participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an adverse event form, which must be submitted within 24 hours of awareness of the event.

Events of serious hypersensitivity that are Grade 3 or higher or lead to treatment discontinuation will be monitored as AESIs during this study.

During the course of the study, additional AESIs may be identified by the Sponsor.

Adverse events of special interest must be recorded in the eCRF.

9.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalizations.

  Note: Any hospitalization requiring admission for at least 1 day or an overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time informed consent is obtained until Week 28 must be reported to [redacted] within 24 hours of the knowledge of the occurrence. Should the patient terminate the study early, SAEs should be reported up until the Early Termination visit or 90 days after the last administration of study drug, whichever is later. After the reporting window, any SAE that the Investigator becomes aware of and is considered related to study drug should be reported to [redacted] or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at

[redacted] or call [redacted] (phone number listed below), and fax/email the completed paper SAE form to [redacted] (contact information listed in Section 9.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

All SAEs must be followed with appropriate medical management until resolved or stabilized.

The site Investigator is responsible for promptly notifying the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or equivalent in accordance with local regulations of all SAEs.

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any patient must be made available to the study monitor.

New or updated information will be recorded in the EDC system. For the purpose of reporting, significant follow-up information corresponds to new medical or administrative information that could impact the assessment or management of a case or could change its seriousness criteria.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to [redacted] via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for the initial reporting of SAEs.

9.4 Pregnancy Reporting

If a patient becomes pregnant during the study following administration of study drug or within 90 days following the last dose, the Investigator is to stop dosing with study drug immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

Pregnancy is not considered to be an adverse event or SAE; however, it must be reported to [redacted] within 24 hours of knowledge of the pregnancy. [redacted] will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted].

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within 90 days following the last dose, the Investigator should notify [redacted] as described above and obtain informed consent for the collection of information regarding the pregnancy.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to [redacted]. If the outcome of the pregnancy meets the criteria for immediate

classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.5 Expedited Reporting

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the relevant authorities in all the countries concerned, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case.

All other SUSARs (except fatal/life-threatening) will be reported to the relevant authorities as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

When an event is considered to be a SUSAR, the blind will be broken by [redacted] for that specific patient. The blind will be maintained for persons responsible for the ongoing conduct of the study.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all investigators as required per local regulation.

The requirements above refer to the requirements relating to the investigational medicinal product.

Expedited reporting of SUSARs related to non-investigational medical products (NIMPs) is not required. All SARs, regardless of expectedness, will be reported to the manufacturer of the marketed product. Line listings of cases related to NIMPs will be included in the Development Safety Update Report.

9.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, an overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of the investigational product are not considered reportable as medication error.

- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations report form will only be completed if a complaint is associated with an ADR.

All special situation events as described above must be reported on the special situations report form and faxed/emailed to [redacted] (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situation reports should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: [redacted]

9.7 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 (United States only) at non-dosing day visits. See Appendix B for a complete list of laboratory analytes.

9.8 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 (United States only) at non-dosing day visits.

9.9 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 (United States only) at non-dosing day visits.

9.10 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 (United States only) at non-dosing day visits.

9.11 Cytomegalovirus Serology

Cytomegalovirus serology will be tested using an enzyme immunoassay to detect CMV antibodies (immunoglobulin G) at Screening. Cytomegalovirus serology will be tested at the local laboratory within 90 days of Randomization to determine eligibility for the study.

9.12 Serum NPC-21 Concentration Measurement

Blood will be drawn on Day 1 and at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, and 28 for serum NPC-21 concentration measurement. On dosing days (Day 1 and at Weeks 4, 8, and 12), blood samples will be collected within 2 hours prior to study drug administration and at 2 hours (±30 minutes) following the beginning of the infusion (Note: Sample collection time points at each visit may be updated based on each administration data). Samples may be collected by home healthcare services (United States only) at non-dosing day visits.

10 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, the percentage of patients with 95% confidence intervals in each category as descriptive statistics. Statistical tests will be 2-sided at the α=0.05 significance level. The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable will be presented in the Statistical Analysis Plan.

Changes in study visit schedules, missed or delayed visits, or patient discontinuations and the relationship to COVID-19 will be captured in the eCRFs. Protocol deviations in study procedures due to COVID-19 will be reported in the Clinical Study Report.

10.1 Analysis Populations

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

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.

The 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.

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

10.2 Statistical Methods

10.2.1 Analysis of Efficacy

The mITT Population will be used for all efficacy analyses.

The primary efficacy endpoint will be the proportion of patients with the occurrence of CMV disease (CMV syndrome [see Appendix C for definition of CMV syndrome] or tissue-invasive CMV disease [see Appendix D 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. 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 the Statistical Analysis Plan. Sensitivity analysis may be performed to assess the impact of these patients on analysis results.

The primary efficacy endpoint will be summarized by treatment group and compared across placebo and the 6 mg/kg NPC-21 treatment group using a logistic regression analysis with stratification factor of region (United States or Japan) as a covariate.

Other efficacy endpoints will be summarized descriptively by treatment group using the mITT Population.

10.2.2 Analysis of Pharmacokinetics

Serum concentrations of NPC-21 will be summarized using descriptive statistics. 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.

10.2.3 Analysis of Exposure-Response

Exposure-response analyses will be performed to propose target concentrations using PK parameters estimated by population-PK, efficacy variables, and biomarkers.

10.2.4 Analysis of Safety

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 adverse events reported during the study.

The number and percentage of patients experiencing treatment-emergent adverse events will be summarized. Summaries will be produced for each body system, as well as for each preferred term using the Medical Dictionary for Regulatory Activities. The number and percentage of patients experiencing SAEs will also be summarized.

10.2.5 Interim Analysis

No interim analysis is planned.

10.2.6 Data and Safety Monitoring Board

The safekeeping and monitoring of data collection will be performed by an independent third party DSMB. The DSMB will be independent of the Sponsor, contract research organization, study Investigators, and anyone involved in the care or evaluation of study patients. Members of the DSMB will not have scientific, financial, or other conflicts of interest related to the Sponsor or Investigators.

The 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.

10.2.7 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 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.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

11.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and adverse events
- WHO Drug Dictionary for prior and concomitant medications

11.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

11.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor. For Japanese sites, no drug will be released to the site for dosing until execution of contract with the study site.

12.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

12.4 Subject Card

On enrollment in the study, the patient will receive a subject card to be carried at all times. The subject card will state that the patient is participating in a clinical research study, type of treatment, number of intravenous infusions received, and contact details in case of an SAE.

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, the Japanese Ministerial Ordinance on GCP for Drugs, Directive 2001/20/EC, and the Declaration of Helsinki, where applicable, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents, and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

12.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, Japanese health authorities, namely Pharmaceuticals and Medical Devices Agency, the Sponsor or their designee, other applicable foreign health authorities, and the IRB/IEC as appropriate. Patients may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or the Sponsor.

12.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has obtained patient liability insurance for all patients who have given their consent to the clinical study. This coverage is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution. The clinical trial compensation guidelines established by the Sponsor is applied.

12.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinions have been received.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

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APPENDIX A: SCHEDULE OF PROCEDURES

	Scr[a]	Treatment Period[b,c,d]																	Observation Period[d,e]					
Study Week	**-2 to 0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 18 19**	**20**	**21 22 23**	**24**	**26**	**28/ ET[f]**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120 127 134**	**141**	**148 155 162**	**169**	**183**	**197**
Visit Window			**±3 days**																					
Assessment																								
Informed consent	X																							
Pre-Randomization[g]	X																							
Randomization[h]	X[i]	X[i]																						
CMV serology[j]	X																							
Transplantation	X																							
Inclusion/exclusion criteria	X																							
Demographics	X																							
Medical/surgical history and present illness	X																							
Prior/concomitant medications[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																							
Body weight[k,l]	X[m]	X[n]				X[n]				X[n]				X[n]				X		X		X		X
Physical examination[k]	X	X[n,o]	X	X	X	X[n]				X[n]				X[n]				X		X		X		X
Vital signs[k,p]	X	X[n,o]	X	X	X	X[n]	X	X	X	X[n]	X	X	X	X[n]	X	X	X	X	X	X	X	X	X	X
Blood biochemistry, hematology, coagulation, and urinalysis[k,q]	X	X[n]	X	X		X[n]		X		X[n]		X		X[n]		X		X		X		X		X

	Scr[a]	Treatment Period[b,c,d]																Observation Period[d,e]					
Study Week	**-2 to 0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17 18 19**	**20**	**21 22 23**	**24**	**26**	**28/ ET[f]**
Study Day	**-14 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120 127 134**	**141**	**148 155 162**	**169**	**183**	**197**
Visit Window			±3 days																					
Assessment																								
FSH, pregnancy test[r]	X																							X
CMV DNA (central laboratory)[k,s]		X^n	X	X	X	X^n	X	X	X	X^n	X	X	X	X^n	X	X	X	X	X	X	X	X	X	X
CMV DNA or antigenemia tests (local laboratory)[t,u]	X	X^n	X	X	X	X^n	X	X	X	X^n	X	X	X	X^n	X	X	X	X	X	X	X	X	X	X
12-lead ECG[k,v]	X					X^n				X^n				X^n				X		X		X		X
Adverse event assessment[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration[w]		X				X				X				X										
Serum NPC-21 concentration measurement[k,x]		X^y	X	X	X	X^y		X		X^y		X		X^y		X		X		X		X		X
Anti–NPC-21 antibody measurement[k,z]		X^n				X^n				X^n				X^n				X						X
Screening for resistant strains analysis[k,aa]		X^n																X						X
EQ-5D-5L[k]		X^n																X						X

a. Screening procedures will take place up to 14 days prior to first study drug administration.
b. The Treatment Period will begin as soon as practical post-transplant but no later than 7 days post-transplant.
c. During the Treatment Period, visits on dosing days (Day 1 and at Weeks 4, 8, and 12) should be conducted in person. Visits on non-dosing days of the Treatment Period (Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, and 16) may be conducted by home healthcare services (United States only). Home healthcare services may perform the following procedures at non-dosing day visits: record concomitant medications, obtain body weight, perform physical examination, record vital signs, collect samples for analysis by the central laboratory, perform 12-lead ECG, perform EQ-5D-5L, and record adverse events.
d. 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 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 the Early Termination Visit and Withdrawal Procedures. Note: Collection of blood samples for serum NPC-21 concentration measurement at Weeks 4, 8, and 12 during the Rescue Phase will be handled in the same manner as visits without study drug administration. Note: If the patient is negative for CMV viremia or has recovered from CMV disease before 4 StudyWeeks have passed following last study drug administration, weekly scheduled visits are not required. The Rescue Phase visits may be conducted by home healthcare services (United States only). Home healthcare services may perform the following procedures at non-dosing day visits: record concomitant medications, obtain body weight, perform physical examination, record vital signs, collect samples for analysis by the central laboratory, perform 12-lead ECG, perform EQ-5D-5L, and record adverse events. The Rescue Phase procedures may be performed at the next scheduled visit after detecting CMV viremia or CMV disease with or without anti-CMV agents per local standard of care. Some Investigators may prescribe anti-CMV agents (eg, VGCV) in advance and instruct the patient to start taking the drug as soon as possible for safety if the disease or viremia develops. If this is the case, the Rescue Phase procedures may be performed at the next scheduled visit. The following procedures will be performed upon entering the Rescue Phase: record the rescue in IRT, record concomitant medications, record the date and reason for entering the Rescue Phase, perform complete physical examination, collect blood sample for CMV DNA analysis by the central laboratory, collect blood samples that will be stored for screening for resistant strains analysis, perform EQ-5D-5L, and record adverse events.
Note: During the 12-week Observation Period, visits at Weeks 17, 19, 21, and 23 may be missed due to unavoidable circumstances (eg, holidays, natural disasters). However, every attempt should be made to ensure a visit occurs. In this case, study staff will make contact with the patient to evaluate their condition, eg, review concomitant medications, any new adverse events since the last visit.

e. During the Observation Period, home healthcare services (United States only) may be utilized at Weeks 17, 18, 19, 20, 21, 22, 23, 24, 26, and 28. Home healthcare services may perform the following procedures at non-dosing day visits: record concomitant medications, obtain body weight, perform physical examination, record vital signs, collect samples for analysis by the central laboratory, perform 12-lead ECG, perform EQ-5D-5L, and record adverse events.
f. For patients who are withdrawn from the study prior to completion, all Week 28 procedures will be performed at an ET visit.
g. 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).
h. 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. If the patient is found to be ineligible during Screening, the dropout procedures will be carried out promptly.
i. Perform Randomization on Day -1 or Day 1 prior to first study drug administration.
j. CMV serology will be tested using an enzyme immunoassay to detect CMV antibodies (IgG). CMV serology will be tested at the local laboratory within 90 days of Randomization to determine eligibility for the study.
k. May be performed by home healthcare services (United States only) 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, the Early Termination visit, and at Rescue Phase visits.
l. In case of hemodialysis patients, body weight is defined immediately after dialysis or dry weight. In case of peritoneal dialysis patients, body weight is defined after removal of dialysate or dry weight.
m. Body weight measured within 7 days prior to pre-Randomization is permitted.
n. Perform prior to study drug administration.
o. Perform within 1 hour of the end of the infusion.
p. Vital signs will include systolic and diastolic blood pressure, pulse rate, and body temperature.
q. Blood biochemistry includes liver function tests and enzymes. Hematology includes complete blood count with differential. Urine samples will be collected if possible. 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 (United States only) at non-dosing day visits.
r. A urine or serum pregnancy test will be performed at Screening and at Week 28 for all females of childbearing potential, and they must have a negative test result. An FSH test will be performed for females of non-childbearing potential (if necessary) at Screening. If a female patient of childbearing potential discontinues the study early, a urine or serum pregnancy test will be performed at the ET visit.
s. Collect blood samples for CMV DNA analysis utilizing PCR analysis. The central laboratory will perform CMV PCR analysis. Samples for evaluation by the central laboratory may be collected by home healthcare services (United States only) at non-dosing day visits.

t. Collect blood samples for CMV DNA or antigenemia testing. The local laboratory will perform CMV PCR analysis or CMV antigenemia testing consistently throughout the study.
u. In the case home healthcare services (United States only) are utilized, it is not necessary to collect blood samples for CMV DNA analysis or CMV antigenemia testing for analysis by the local laboratory.
v. Additional follow-up ECGs may be performed if clinically indicated.
w. Administer NPC-21 (at a dose of 6 or 12 mg/kg of actual body weight [at Screening]) or placebo via an approximately 60-minute intravenous infusion at a constant rate of 5 mL/minute (Note: If an adverse event occurs during study drug administration and the Investigator deems it necessary, deceleration, suspension, or resumption of study drug administration is allowed).
x. Collect blood sample for serum NPC-21 concentration measurements. Samples may be collected by home healthcare services (United States only) at non-dosing day visits.
y. 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 (Note: Sample collection time points at each visit may be updated based on each administration data).
z. Collect blood samples for anti–NPC-21 antibody measurements. Samples may be collected by home healthcare services (United States only) at non-dosing day visits.
aa. Collect blood samples that will be stored for screening for resistant strains analysis. Samples may be collected by home healthcare services (United States only) at non-dosing day visits.

CMV = cytomegalovirus; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels questionnaire; ET = Early Termination; FSH = follicle-stimulating hormone; IgG = immunoglobulin G; IRT = Interactive Response Technology; PCR = polymerase chain reaction; Scr = Screening; US = United States; VGCV = valganciclovir.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Blood urea nitrogen
Calcium	Chloride
C-reactive protein	Creatine kinase
Creatinine	Direct bilirubin
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	Indirect bilirubin
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total cholesterol	Total protein
Triglycerides	Uric acid

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
Reticulocyte	White blood cell count and differential [1]

1. Neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

Coagulation

Activated partial thromboplastin time	International normalized ratio
Prothrombin time	

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [2]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

2. Microscopy is performed only as needed based on positive dipstick test results.

Pregnancy Tests (Female Patients of Childbearing Potential Only)

Urine or serum

Endocrinology (Postmenopausal Female Patients Only)

Follicle-stimulating hormone [3]

3. Follicle-stimulating hormone in postmenopausal female patients, with spontaneous amenorrhea for at least 2 years, to confirm their postmenopausal status.

APPENDIX C: THE DEFINITION OF CYTOMEGALOVIRUS SYNDROME

Cytomegalovirus Syndrome

Cytomegalovirus (CMV) syndrome is a disease definition that should only be used in solid organ transplant recipients. Because it is impossible to exclude all other causes of the clinical symptomatology described as CMV syndrome, a "proven" category cannot be defined. The definition of probable CMV syndrome requires detection of CMV in blood by viral isolation, rapid culture, antigenemia, or nucleic acid testing together with at least 2 of the following:

1. Fever ≥38°C for at least 2 days.
2. New or increased malaise (toxicity Grade 2) or new or increased fatigue (toxicity Grade 3) (National Cancer Institute: Common Terminology Criteria for Adverse Events, version 4.0).
3. Leukopenia or neutropenia on 2 separate measurements at least 24 hours apart, defined as a white blood cell (WBC) count of <3500 cells/μL, if the WBC count prior to the development of clinical symptoms was ≥4000 cells/μL, *or* a WBC decrease of >20%, if the WBC count prior to the development of clinical symptoms was <4000 cells/μL. The corresponding neutrophil counts are <1500 cells/μL or a decrease of >20% if the neutrophil count before the onset of symptoms was <1500 cells/μL.
4. Greater than or equal to 5% atypical lymphocytes.
5. Thrombocytopenia defined as a platelet count of <100,000 cells/μL if the platelet count prior to the development of clinical symptoms was ≥115,000 cells/μL or a decrease of >20% if the platelet count prior to the development of clinical symptoms was <115,000 cells/μL.
6. Elevation of hepatic aminotransferases (alanine aminotransferase or aspartate aminotransferase) to 2 times the upper limit of normal (applicable to non-liver transplant recipients).[1]

Sources:

1. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis.* 2017;64(1):87-91.

APPENDIX D: THE DEFINITIONS OF CYTOMEGALOVIRUS DISEASE

Cytomegalovirus Disease Definitions

The definitions of cytomegalovirus disease are provided in Ljungman et al.[1]

Sources:

1. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis*. 2017;64(1):87-91.