A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of a Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seronegative Kidney Transplant Recipients Receiving an Organ from a CMV-Seropositive Donor

ISN/Protocol 0113-CL-2001

ClinicalTrials.gov Identifier: NCT01974206

Date of Protocol: Final Version 3.0, 06 Jan 2014

Sponsor: Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

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Protocol for Phase 2 Study of ASP0113

ISN/Protocol 0113-CL-2001

Version 3.0

Incorporating Substantial Amendment 2 [See Attachment 1]

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

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Original Version 1.0 [29Apr2013]
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I. SIGNATURES

1. SPONSOR'S SIGNATURE

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of a Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seronegative Kidney Transplant Recipients Receiving an Organ from a CMV-Seropositive Donor

ISN/Protocol 0113-CL-2001 / Version 3.0

Incorporating Substantial Amendment 2 / 06 January 2014

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors, etc.) are located in Section 14 Sponsor's Signatures; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of a Vaccine, ASP0113, in Cytomegalovirus (CMV)-seronegative Kidney Transplant Recipients Receiving an Organ from a CMV-seropositive Donor

ISN/Protocol 0113-CL-2001 / Version 3.0

Incorporating Substantial Amendment 2 / 06 January 2014

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD MMM YYYY)

Printed Name: ----------

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.6**	[redacted], MD, FACS [redacted] **Main Office:** [redacted] **Cell:** [redacted] **Please fax the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Product Safety & Pharmacovigilance** **Fax number:** [redacted] **International Fax:** [redacted] **Email:** [redacted]
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III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of Abbreviations
ABMR	Antibody Mediated Rejection
AC	Adjudication Committee
AE	Adverse Event
aGVHD	Acute Graft-versus-host Disease
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
APEBV	Astellas Pharma Europe B.V.
APGD	Astellas Pharma Global Development, Inc.
AREC	Astellas ethical committee
AST	Aspartate Aminotransferase (GOT)
ASP0113	DNA vaccine encoding the two CMV plasmids gB and pp65
AT	Aminotransferase
ATG	Anti-thymocyte Globulin
ATN	Acute Tubular Necrosis
AUST	Astellas US Technologies, Inc.
AVT	Antiviral Therapy
AVP	Antiviral Prophylaxis
BAK	Benzalkonium Chloride
BAL	Bronchoalveolar Lavage
BKVAN	BK Virus Associated Nephropathy
BPAR	Biopsy Proven Acute Rejection
BPP	Bayesian predictive probability
BUN	Blood Urea Nitrogen
CA	Competent Authorities
cGVHD	Chronic Graft-Versus-Host-Disease
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine Kinase
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
DDC	Deceased Donor Criteria
DILI	Drug-induced Liver Injury
dL	Deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid

Abbreviations	Description of Abbreviations
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-linked Immunosorbent Assay
ELISPOT	Enzyme-linked Immunosorbent Spot
EOD	End Organ Disease
EQ-5D	EuroQol – 5 dimensions 5 levels
ER	Emergency Room
EU	European Union
EudraCT	European Union Drug Regulatory Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSI	First Subject In
gB	Glycoprotein B
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPF	Global Protocol Format
GWAS	Genome-Wide Association Studies
hCG	Human Chorionic Gonadotropin
H_0	Null Hypothesis
H_1	Alternative Hypothesis
HBV	Hepatitis B Virus
HCT	Hematopoietic Cell Transplant
HCV	Hepatitis C Virus
HEA	Health Economics Assessment
HEOR	Health Economics and Outcomes Research
HHC	Home Healthcare
HHV	Human Herpes Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICD-9	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFN-γ	Interferon Gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug

Abbreviations	Description of Abbreviations
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Study Number
ITT	Intent-to-treat
IU	International Unit
IUD	Intra Uterine Device
IUS	Intra Uterine System
IV	Intravenous
IVIG	Intravenous Immunoglobulin
KTQ	Kidney Transplant Questionnaire
L	Liter
LA CRF	Liver Abnormality Case Report Form
LDT	Laboratory Developed Test
LFT	Liver Function Tests
LLOQ	Lower Limit of Quantitation
LSO	Last Subject Out
MAA	Marketing Authorization Application
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
m^2	Millimeter squared
MMF	Mycophenolate mofetil
mmHg	Millimeters of Mercury
NASH	Non Alcoholic Steatohepatitis
NCI-CTCAE	National Institutes of Health Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NK	Natural Killer
PBS	Phosphate-buffered Saline
PCR	Polymerase Chain Reaction
PCS	Potentially Clinically Significant
PE	Physical Examination
PGS	Pharmacogenomics Set
PGx	Pharmacogenomics
PHI	Protected Health Information
PK	Pharmacokinetic
PO	Per Os (oral)
PP	Per Protocol
pp65	Phosphoprotein 65
PPS	Per Protocol Set
pPRO	Paper Patient Reported Outcomes
PTLD	Post Transplant Lymphoproliferative Disorder
QOL	Quality of Life
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Analysis Set

Abbreviations	Description of Abbreviations
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SF-12	ShortForm-12 Health Survey
SOP	Standard Operating Procedure
SOT	Solid Organ Transplant
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TCMR	T-Cell Mediated Rejection
TE	Treatment-emergent
TEAE	Treatment-emergent Adverse Event
TLFs	Tables, Listings and Forms
TMF	Trial Master File
ULN	Upper Limit of Normal
VZV	Varicella Zoster Virus
WBC	White Blood Cell
WHO	World Health Organization

Definition of Key Study Terms

Terms	Definition of terms
Adverse Event	An adverse event is any untoward medical occurrence in a subject who was administered a Study Drug or has undergone study procedures that does not necessarily have a causal relationship with the treatment.
Adverse Reaction	An adverse reaction means any adverse event caused by a drug.
Baseline	Baseline is the time point prior to the first dose of randomized Study Drug. Visit 2 is considered the Baseline Visit in this study. The last measurement / evaluation prior to the first dose of randomized therapy is considered the baseline measure/evaluation.
CMV Infection	Replication of CMV (isolation of the virus or detection of viral protein or nucleic acid in any body fluid or tissue).
CMV End Organ Disease (EOD)	As defined in Appendix 7.
CMV Syndrome	As defined in Appendix 7.
CMV Viremia	Presence of CMV in the blood.
End of Study	The point in time when the last protocol-defined assessment has been completed (end of the Long-term Follow-up Period).
End of Treatment	The point in time when the subject receives the last dose of Study Drug.
Enrollment	The point in time when the subject signs the informed consent.
Evaluable Subject	A subject who meets all inclusion criteria and does not meet any exclusion criteria and who has received at least one injection of Study Drug.
Long-term Follow-up Period	The period of time from the Day 395 Visit (Visit 13) through the completion of the 4½ year additional safety follow-up.
Long-term Follow-up Withdrawal	A subject who completes the Primary Study Period but does not complete the Long-term Follow-up Period for any reason.
Preemptive Therapy	A therapeutic treatment regimen where treatment for an infection/disease is initiated only after it is detected/confirmed.
Primary Follow-up Period	The period of time from the end of the Study Drug treatment through the Day 395 Visit (Visit 13).
Primary Study Period	The period of time from enrollment (i.e., signing of informed consent) through the Day 395 Visit (Visit 13).
Primary Study Withdrawal	A subject who is randomized but does not complete the Primary Study Period for any reason.
Principal Investigator	A physician or a Pharm D approved by Astellas responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the Principal Investigator is the responsible leader of the team.
Prophylactic Therapy	A therapeutic treatment regimen where treatment is administered prior to the detectable presence of infection or disease as a preventative measure.

Terms	**Definition of terms**
Randomization	The action to allocate a subject to a treatment group. In this study, randomization occurs after the subject has met all inclusion and exclusion criteria between days -14/+30 relative to the transplant date.
Reactogenicity	Local or systemic inflammatory effects relating to the study drug injection.
Screening	The process for identifying a candidate for the study and evaluating their eligibility to participate.
Screen Failure	A subject who signs the informed consent and undergoes the protocol-specific screening procedures, but does not fulfill the protocol inclusion and/or exclusion criteria. This subject should not be randomized.
Serious Adverse Event	An adverse event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: results in death, is life threatening, results in persistent or significant disability / incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, or is a medically important event.
Source Data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.
Source Documents	Original documents, data and records including source data.
Subject	An individual who participates in a clinical trial.
Treatment Period	The period of time from the first dose of Study Drug through the last dose of Study Drug.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	06 January 2014 / Version 3.0
Sponsor: Astellas Pharma Global Development Inc (APGD)	**Protocol Number:** 0113-CL-2001
Name of Study Drug: ASP0113	**Phase of Development:** Phase 2

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of a Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seronegative Kidney Transplant Recipients Receiving an Organ from a CMV-Seropositive Donor

Planned Study Period:

First subject in (FSI) 4Q2013; Last Subject Out (LSO) 2Q2017, (Primary Study Period)
Long-term Follow-up Period LSO 4Q2021

Study Objective(s):

1. To evaluate the efficacy of ASP0113 compared to placebo in reducing the incidence of CMV viremia (defined as plasma viral load ≥ 1000 IU/mL by central laboratory assay) through one year post first Study Drug injection in CMV-seronegative subjects receiving a kidney from a CMV-seropositive donor.
2. To evaluate the safety of ASP0113 in CMV-seronegative subjects receiving a kidney from a CMV-seropositive donor.

Planned Total Number of Study Centers and Location(s):

Approximately 80 sites globally

Locations: Countries may include, but are not limited to: United States, Canada, Germany, Spain, France and Australia

Study Population:

CMV-seronegative subjects who have received a kidney from a living or deceased CMV-seropositive donor.

Number of Subjects to be Enrolled / Randomized:

140 (70 per Treatment Group)

Study Design Overview:

This is a randomized, double-blind, placebo-controlled trial.

140 CMV-seronegative subjects who have received a kidney from a living or deceased CMV-seropositive donor will be randomized 30 days ± 3 days after transplantation (Day 0) in a 1:1 ratio to ASP0113 or placebo.

Prior to Randomization, subjects will be stratified by use of anti-thymocyte globulin and by receipt of a kidney from a living or deceased donor.

Subjects will receive either 5 doses of ASP0113 or 5 doses of placebo on Days 30 ± 3, 60 ± 5, 90 ± 5, 120 ± 5, and 180 ± 5 in relation to the day of transplant.

Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) through the day of Randomization to prevent CMV disease. (The subject can miss up to two doses of valganciclovir or ganciclovir during this time period for any reason).

Subjects will then continue to receive CMV-specific anti-viral prophylaxis (AVP) with valganciclovir or ganciclovir until 100 days post transplant. Subjects can have valganciclovir or ganciclovir interrupted, dose adjusted or replaced by other CMV-specific AVP per standard of care after the day of Randomization if renal function is compromised, there are toxicities related to the administration of the AVP, or for any other medically indicated reason.

In all subjects, plasma will be collected for central laboratory CMV viral load testing every two weeks from Day 100 through Day 200, then monthly through last study visit.

In cases where CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected from the first Study Drug injection through Day 395, a sample for CMV viral load will be collected at the time of the first CMV symptom recognition and sent to a local and the central laboratory.

CMV-specific anti-viral therapy (AVT) should be initiated for CMV disease and can be initiated for CMV viremia based on the central or local laboratory results and standard of care.

If CMV-specific AVT is initiated, a central CMV viral load will be obtained at a minimum of weekly from the time CMV-specific AVT is initiated until discontinuation.

In addition, each time a local CMV viral load sample is collected, a plasma sample will also be collected and sent to the central laboratory for CMV viral load testing.

Subjects will be followed for one year post first Study Drug injection (Study completion/Day 395) for CMV viremia, CMV syndrome, CMV tissue-invasive disease, CMV-specific AVT, graft survival, and subject survival.

Subjects will be followed for one year post first Study Drug injection for resistance to valganciclovir or ganciclovir. Viral resistance will be assessed by a Central lab when there is no reduction in viral load two weeks after initiating valganciclovir/ganciclovir, when there is no improvement in clinical signs and symptoms two weeks after initiating valganciclovir /ganciclovir or any time it is clinically indicated.

Immunogenicity to pp65 and gB will be assessed prior to Dose 1, two weeks after Dose 2, prior to Dose 3, two weeks after Dose 4, prior to Dose 5 and at the last study visit.

Subjects will be evaluated for local and systemic reactogenicity 15 minutes and one hour after each Study Drug injection and for 7 days by subject reporting via diary after each Study Drug injection. All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post first Study Drug injection.

Subjects will be contacted by telephone 6 months after Day 395, then annually for the next 4 years, to evaluate long-term safety related to the deoxyribonucleic acid (DNA) vaccine. Mortality, development of any new malignancies, development of infection requiring hospitalization or resulting in death, graft survival, creatinine and erythema and/or induration at the injection sites will be assessed by questionnaire and available patient records.

An Independent Data Monitoring Committee (DMC) will be chartered to oversee the safety of subjects and review of the futility analysis.

An Adjudication Committee (AC) will be chartered to adjudicate all cases of CMV syndrome, CMV tissue-invasive disease and CMV-specific antiviral therapy.

Inclusion/Exclusion Criteria:

Subjects will be selected based on Inclusion and Exclusion Criteria listed. Waivers to eligibility criteria will not be allowed.

Inclusion:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability (HIPAA) Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-specific procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is willing to comply with the protocol.
3. Subject is ≥ 18 years of age or the legal age of consent (whichever is greater).
4. Subject is CMV-seronegative at time of transplant and has received a kidney from a CMV-seropositive living or deceased donor. CMV serostatus of the recipient can be determined from 8 weeks prior to transplant, by local laboratory, through day of transplantation. If CMV serostatus is not available from this time period, CMV serostatus may be assessed at the Screening Visit, by local laboratory, with results available prior to Randomization.
5. Subject started valganciclovir or ganciclovir within 10 days of transplant and has received it through Randomization, per regulatory label (package insert).
6. Female subject must be either:
   - Of non- child-bearing potential:
     - post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
     - documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening).
   - Or, if of childbearing potential:
     - must have a negative urine pregnancy test at Screening, and
     - if heterosexually active must use two forms of birth control* (at least one of which must be a barrier method) starting at Screening and during the Primary Study Period.
7. Female subject must not be breastfeeding at Screening and during the Primary Study Period.
8. Female subject must not donate ova starting at Screening and during the Primary Study Period.
9. Male subject and his female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control* (one of which must be a barrier method) starting at Screening and during the Primary Study Period.

   *Acceptable forms of birth control include:
   - Established use of oral, injected or implanted hormonal methods of contraception.
   - Placement of intrauterine device (IUD) or intrauterine system (IUS).
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
   - Partner male sterilization (i.e., vasectomy)
10. Male subject must not donate sperm starting at Screening and during the Primary Study Period.
11. Subject agrees not to participate in another interventional drug study while on treatment.

Exclusion:

1. Subject is planned to undergo a course of CMV-specific prophylactic therapy with antiviral drugs with a duration of greater than 100 days.
2. Subject has received from one month prior to transplant or is planning to receive CMV immunoglobulin.
3. Subject has had CMV viremia or CMV disease from time of transplant until time of Randomization.

4. Subject has received, at any time, an organ transplant other than a kidney. (Dual allocation of a kidney is acceptable).
5. Subject requires dialysis on the day of Randomization.
6. Recipient or donor is known to be positive for human immunodeficiency virus (HIV), hepatitis B surface antigen, or hepatitis B core IgM or IgG antibody.
7. Subject is known to have latent or active tuberculosis which has not been adequately treated.
8. Subject required desensitization for ABO blood type incompatibility or a positive T or B cell crossmatch.
9. Subject has received any of the following substances or treatments:
    a. Investigational research products within 28 days or 5 half lives whichever is longer, prior to Transplantation, or subject is scheduled to receive investigational research products through one year after Randomization.
    b. Alemtuzumab within 90 days prior to Randomization or is scheduled to receive alemtuzumab any time through one year post Randomization.
    c. Rituximab within 120 days prior to Randomization or is scheduled to receive rituximab any time through one year post Randomization.
    d. Eculizumab or bortezomib from the Day of Transplantation through the Day of Randomization or is scheduled to receive eculizumab or bortezomib any time through one year post Randomization.
    e. IVIG and/or plasmapheresis from Day of Transplant through Day of Randomization.
    f. Live attenuated vaccines within one month (30 days) prior to the first dose of Study Drug or is scheduled to receive live attenuated vaccines within one month of any Study Drug injection.
    g. Subunit or killed vaccines within 14 days prior to the first dose of Study Drug or is scheduled to receive a subunit or killed vaccine within 14 days prior to any Study Drug injection.
    h. Administration of a CMV vaccine, including any prior exposure to ASP0113.
    i. Subject has received the following anti-viral therapies or it is planned for them to receive the AVT for prophylaxis of viral infections in excess of the following doses from time of transplant through Randomization:
        - *Aciclovir:* 1600 mg orally (total daily dose), or 500 mg/m^2/dose Intravenous (IV) (total daily dose)
        - *Valaciclovir:* 1000 mg orally (total daily dose)
        - *Famciclovir:* 500 mg orally (total daily dose)
10. Subject has received any anticoagulants including, but not limited to, vitamin K antagonists, heparin or its derivatives, low molecular weight heparin, factor X inhibitors, or thrombin inhibitors within 5 half-lives prior to Randomization or is expected to use anticoagulants within 5 half-lives prior to any Study Drug injection. Low dose anticoagulants that are used for prevention of deep vein thrombosis and antiplatelet agents are allowed.
11. Subject has any contraindication to or cannot be dosed with valganciclovir or ganciclovir per package insert on the Day of Randomization for any reason.
12. Subject has, or is expected to have during the Primary Study Period, a contraindication to an intramuscular injection.
13. Subject, within 3 days prior to Randomization, has an Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) greater than 3 x Upper Limits of Normal (ULN) or total bilirubin greater than 2 x ULN unless secondary to suspected Gilbert's disease.

14. Subject has a current malignancy or a recent history of malignancy (within the past 5 years prior to Screening) except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully or cancer *in situ* of the cervix uteri that has been successfully treated by local therapy.
15. Subject is being treated for an active infection at the time of Randomization.
16. Subject has any condition or an unstable medical or psychiatric condition, including a history of illicit drug(s) or alcohol abuse that the Investigator believes will place the subject at unacceptable risk or interfere with compliance to protocol requirements.
17. Subject has any other condition which, in the opinion of the Investigator, precludes the subject's participation in the trial.
18. Subject has known allergies or previous adverse reactions to ganciclovir or valganciclovir.
19. Subject has had an allergic reaction to any component of the vaccine, or to aminoglycosides, as kanamycin is used during the manufacturing process of the vaccine.

Investigational Product(s):
ASP0113

Dose(s):
1 mL of a 5mg/mL solution of ASP0113 will be administered intramuscularly (IM) in the deltoid muscle, alternating sides with each dose, if possible.

Subjects will receive five injections of ASP0113 over an approximately 5 month period.

Mode of Administration:
Intramuscular (IM)

Comparator:
The Placebo is phosphate-buffered saline (PBS)

Dose(s):
1 mL administered IM in the deltoid muscle alternating sides with each dose, if possible. Subjects will receive five injections of Placebo over an approximately 5 month period.

Mode of Administration:
Intramuscular (IM)

Concomitant Medication Restrictions or Requirements:

Concomitant Medications and Therapies

CMV Prophylaxis

Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) through Randomization to prevent CMV disease. (The subject can miss up to two doses of valganciclovir or ganciclovir during this time period for any reason). After Randomization, subjects will then receive CMV-specific AVP with valganciclovir or ganciclovir until 100 days post transplant. Subjects can have valganciclovir or ganciclovir interrupted, dose adjusted or replaced by other CMV-specific AVP per standard of care after the Day of Randomization if renal function is compromised, there are toxicities related to the administration of the AVP, or for any other medically indicated reason.

Viral Prophylaxis

Viral prophylaxis for infection other than CMV should be administered according to standard institutional protocols. Prophylactic use of aciclovir (acyclovir), valaciclovir (valacyclovir), or

famciclovir should not exceed the following doses following transplant (Day 0) through one year post first Study Drug injection (Day 395/Visit 13).

Aciclovir: 1600 mg orally (total daily dose), or 500 mg/m^2/dose IV (total daily dose)

Valaciclovir: 1000 mg orally (total daily dose)

Famciclovir: 500 mg orally (total daily dose)

These doses may be exceeded if necessary to treat active infections.

<u>*Pneumocystis jiroveci* Pneumonia Prophylaxis</u>

Pneumocystis jiroveci pneumonia prophylaxis must be initiated for all study participants according to the site's standard practice for kidney transplant recipients and applied uniformly to all enrolled subjects. Dose may be adjusted or therapy interrupted for renal dysfunction, adverse events related to the administration of the therapy or for other clinically indicated reasons. If there is no prophylactic Pneumocystis protocol, the investigator must decide on appropriate *Pneumocystis jiroveci* pneumonia prophylaxis.

Prohibited Concomitant Medications (Drugs and Therapies):

- Investigational research products through completion of Day 395 visit (Visit 13).
- Planned Alemtuzumab and, anti-CD20 antibodies (including rituximab), eculizumab or bortezomib are not allowed from the Day of Randomization through the Primary Study Period (Day 395). These treatments may be given after the Day of Randomization if clinically indicated.
- Prophylactic use of CMV immunoglobulin.
- Live attenuated vaccines within one month (30 days) prior to each dose of Study Drug.
- Subunit or killed vaccines within 14 days before any Study Drug injection.
- Anticoagulants, within 5 half-lives of Study Drug administration, including but not limited to vitamin K antagonists, heparin or its derivatives, low molecular weight heparin, factor X inhibitors, or thrombin inhibitors. Low dose anticoagulants that are used for prevention of deep vein thrombosis and antiplatelet agents are allowed.

Duration of Treatment:

Subjects will receive either 5 doses of ASP0113 or 5 doses of placebo on Days 30 ±3, 60 ±5, 90 ±5, 120 ±5, and 180 ±5 in relation to the day of transplant.

Discontinuation Criteria:

Study and Treatment Discontinuation

Subjects will be withdrawn from investigational study treatment and all follow up assessments and will only be followed for mortality through public records if the following occurs:

- Withdrawal of consent by the subject.

Treatment Only Discontinuation

Subjects should continue to be followed according to the study Schedule of Assessments and Long Term Follow-up Schedule of Assessments, except post-dose Day 14 safety and laboratory and reactogenicity assessments/visits for those doses not given, but will be withdrawn from investigational study treatment if any of the following occur:

- Investigator's decision that further treatment is not in the best interest of the subject.
- Graft failure
- Pregnancy (female subjects only).

- Local reactogenicity with a grade ≥ 3 based on the criteria defined in appendices and confirmed by a health care professional.
- Systemic reactogenicity for any grade ≥ 3 fever or any other grade 4 systemic reaction within one week of vaccination and confirmed by a health care professional.
- Anaphylaxis Grade ≥ 3 per NCI ver. 4.03 criteria.

Long Term Follow-up Period

Subjects will only be followed for mortality through public records in case of withdrawal of consent by the subject.

Endpoints for Evaluation:

Primary Efficacy

Incidence of CMV viremia (defined as plasma viral load of ≥ 1000 IU/mL by central assay) through one year post first Study Drug injection.

Secondary Efficacy

Incidence of:

- Adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease through one year post first Study Drug injection.
- CMV viremia (defined as plasma viral load ≥ the lower limit of quantification [LOQ]) by central assay through one year post first Study Drug injection.
- Adjudicated CMV-specific antiviral therapy for the treatment of CMV viremia or disease through one year post first Study Drug injection.
- Graft survival through one year post first Study Drug injection.
- Subject survival through one year post first Study Drug injection.

Exploratory Efficacy

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ 1000 IU/mL by central assay) through one year post study first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of CMV viral load of ≥ 1000 IU/mL by central assay through one year post first Study Drug injection.
- Peak CMV viral load through one year post first Study Drug injection.
- Viral load area under the curve (AUC), as a measure of "cumulative viral load" through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV- associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of viral resistance to ganciclovir or valganciclovir through one year post first Study Drug injection as determined by a central laboratory assay.
- Incidence of biopsy-proven (T or B cell) rejection (BPAR) (Banff 2007 Grade ≥ 1) through one year post first Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at the last study visit, calculated using the 4 variable Modification of Diet in Renal Disease (MDRD) formula.

- Incidence of clinically treated acute graft rejection through one year post first Study Drug injection.
- Patient-reported outcomes through one year post first Study Drug injection:
  - EuroQol-5 dimensions 5 levels (EQ-5D)
  - Kidney Transplant Questionnaire (KTQ)
  - Short Form Health Survey version 2 (SF-12v2)
- Healthcare resource utilization through one year post first Study Drug injection:
  - Resource use will be collected including the following: .hospitalizations recorded as number of days in the Intensive Care Unit, Step-down Unit, and general medical ward, (including emergency room visits greater than 24 hours), also non -protocol -related physician visits and emergency room visits of less than 24 hours.

Immunogenicity Variables

- T-cell responses to pp65 through one year post first Study Drug injection.
- gB-specific antibody levels through one year post first Study Drug injection.

Safety Assessments

- Vital signs
- Adverse events using the National Institutes of Health Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 4.03 grading scale
- Local reactogenicity signs and symptoms using both the NCI-CTCAE v. 4.03 grading scale and the protocol-specified reactogenicity scale
- Systemic reactogenicity signs and symptoms using both the NCI-CTCAE v. 4.03 grading scale and the protocol-specified reactogenicity scale
- Clinical laboratory assessments as defined in Appendices
- Physical examination

Statistical Methods:

Sample Size Justification:

In a recent study of prophylactic valganciclovir given at 900 mg/day for 100 days to donor CMV-seropositive/recipient CMV seronegative (D+R-) kidney transplant recipients (Humar, 2006), CMV viremia, defined as CMV viral load > 600 copies/mL, was seen through one year in 83 of 163 subjects [50.9%, 95% CI = (43.0%, 58.8%)]. In another study (Couzi, 2012), CMV infection, defined as two consecutive positive Polymerase Chain Reaction (PCR) assay results, was seen in 11 of 32 subjects [34.4%, 95% Confidence Interval (CI) = (18.6%, 63.2%)], respectively. Pooled from these two studies by weighted average, it is estimated that placebo rate is 46% (70% weight on Humar's result). A sample size of 64 subjects per arm will allow the study to have 80% power to detect a reduction in CMV viremia to 25% due to ASP0113 at 52 weeks using a 1-sided test with a type 1 error rate of 5%. To allow for loss to follow-up, 70 subjects per arm will be enrolled for a total sample size of 140 subjects.

Efficacy:

The Full Analysis Set (FAS) to be used for primary analysis of the primary efficacy variable will consist of all randomized subjects who receive at least one Study Drug injection and have at least one post dose viral load assessment by central laboratory. The FAS will be used for all efficacy analyses.

The primary analysis of the incidence of CMV viremia will consist of a Cochran-Mantel-Haenszel (CMH) test stratified by the factors used in the stratified randomization. Subjects who are lost to follow-up will be assumed to have met the primary endpoint. The secondary variables will each be similarly analyzed.

The event rates of the secondary variables will each be compared between treatments using the same CMH method as in the primary analysis. The survival endpoints (time to first event) will be analyzed using a Cox proportional hazards model. The Cox model will include the randomization factors. The common hazard ratio and confidence limits will be estimated. The 1-sided p-values for testing the hypothesis that the hazard ratio is equal to unity will be calculated. The Kaplan-Meier survival curves for the treatment groups will be displayed.

Pharmacogenomics:

Subjects who consent to participate in the optional pharmacogenomics sub-study will have a whole blood sample collected during the Baseline visit, after Randomization but prior to the first Study Drug injection, for exploratory retrospective pharmacogenomics (PGx) analysis.

Safety:

The safety analysis set will consist of all randomized subjects who have received at least one Study Drug injection. This analysis set will be used for all summaries of adverse events, reactogenicity, clinical lab data, physical exams, vital signs and subject survival through one year post first Study Drug injection. All recorded AEs will be listed, including duration, outcome, toxicity grade, and association with use of Study Drug.

Interim Analyses:

Two interim safety and efficacy analyses are planned. The first one will occur when 50 subjects (approximately 25 in each group) have completed the month 6 visit assessment. The second interim analysis will occur when 90 subjects (approximately 45 per group) have completed the 6 month visit assessment.

A Data Monitoring Committee (DMC), comprising-individuals who are not on the study team and not investigators, will be established to review safety and efficacy data at each interim look. A detailed description of the DMC, its role in this clinical trial, and the timing of the scheduled reviews will be provided in the DMC Charter.

Data from all subjects who have been enrolled will be included in the safety reviews. All data submitted to the DMC will remain blinded to Astellas personnel involved in the study. A detailed safety data interim analysis plan will be included in the DMC Charter.

Interim efficacy analyses will be performed for the sole purpose of assessing futility. Interim efficacy analyses will include all available data from subjects who have completed the 6 month visit. At each interim, Bayesian predictive probability (*BPP*) that the observed rate of viremia in the ASP0113 treatment group being at least 25% less than the observed viremia rate in the placebo treatment group will be calculated.

If the $BPP \leq 0.20$, it will be concluded that ASP0113 meets futility criterion.

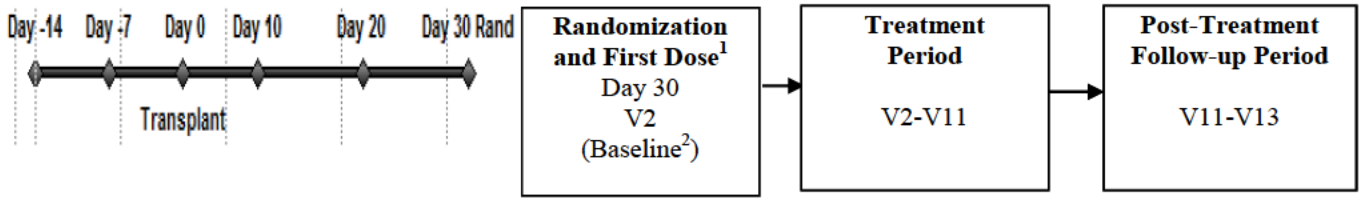
Extensive simulations were conducted to assess the operating characteristics of this futility criterion, and the results are satisfactory. The simulation algorithm, scenarios and results will be summarized in the SAP for this protocol.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

Screening/Informed Consent through Visit 13/Day 395

Screening Period



1. Baseline is date of first dose (Visit 2). The day of transplant is Day 0 and all visit days are relative to Day 0 with the exception of the injection safety follow up visits which are relative to each dose. A visit window is allowed for each visit.
2. Screening and baseline visits may take place on the same day if all clinical labs as measured by the local laboratory meet inclusion and exclusion criteria.

Long-term Follow-up Period: Primary Study Period Completion through Long-term Follow-up Completion (Day 395/Visit 13 through 5.5 years post first Study Drug injection)

Long-term Follow-up Contact*	Long-term Follow-up Contact*	Long-term Follow-up Contact*	Long-term Follow-up Contact*	Long-term Follow-up Contact*
1.5 Years Post first Study Drug injection	2.5 Years Post first Study Drug injection	3.5 Years Post first Study Drug injection	4.5 Years Post first Study Drug injection	5.5 Years Post first Study Drug injection

* Subjects will be contacted by telephone at 6 months after Day 395, then annually for the next 4 years, to evaluate for long-term safety related to the DNA vaccine. Items to be assessed by questionnaire and available patient records are mortality, development of any new malignancies, development of infection requiring hospitalization or resulting in death, graft survival, creatinine and erythema and induration at the injection site. Subjects that discontinue treatment early will be followed per the same schedule.

Table 1: Schedule of Assessments

	Screening[1]	Baseline Randomization and Dose 1		Dose 2		Dose 3		Day 100	Dose 4		Dose 5			Study Completion/ Early Termination[23]
Visit Number	1	2	3*	4	5	6	7*		8	9	10	11*	12	13
Day (From Transplant for dosing visits or prior dose)	-14 through +30 Day of Transplant = Day 0[2]	30	14 days after Dose 1[25]	60	14 days after Dose 2[25]	90	14 days after Dose 3[25]		120	14 days after Dose 4[25]	180	14 days after Dose 5[25]	270	395
Visit Window (days)		+/-3	+/- 3	+/- 5	+/- 3	+/- 5	+/- 3		+/- 5	+/- 3	+/-5	+/- 3	+/- 10	+14
Month		1		2		3			4		6		9	13
Valganciclovir/Ganciclovir[3]	→ By Day 10 Post Transplant													
Informed Consent[4]	X													
Subject Number Assignment[5]	X													
Inclusion/Exclusion Assessment	X	X[P]												
EQ-5D, KTQ, SF-12[6]		X[P]		X[P]		X[P]			X[P]		X[P]			X
Medical History & Demographics[7]	X													
Clinical Evaluation (Physical Exam & Vitals)[8]	X	X[P]		X[P]		X[P]			X[P]		X[P]		X	X
Concomitant Medication Review (including immunosuppressants)[9]	X	X[P]		X[P]	X	X[P]			X[P]	X	X[P]		X	X
Health Economic Assessment (HEA)	X	X[P]		X[P]		X[P]			X[P]		X[P]		X	X
Clinical Laboratories[10]	X	X[P]	X	X[P]	X	X[P]	X		X[P]	X	X[P]	X		X
Urinalysis, with Microscopic Evaluation	X	X[P]	X	X[P]	X	X[P]	X		X[P]	X	X[P]	X		X
Urine:Protein Creatinine Ratio	X	X[P]	X	X[P]	X	X[P]	X		X[P]	X	X[P]	X		X
Pregnancy Test (females)[11]	X	X[P]		X[P]		X[P]			X[P]		X[P]		X	X
CMV Serologies[12]	X													
Adverse Event and SAE Review[13]	X	X[P]		X[P]	X	X[P]			X[P]	X	X[P]		X	X
Transplant Information[14, 15]		X												
Randomization[1]		X[P]												
CMV Plasma Viral Load Testing (see Table 1a)[16, 17, 24]								→ Every 2 Weeks					→ Monthly	
CMV Genotypic Resistance Testing, when applicable[18, 24]			→											
Immunology Lab[19, 24]		X[P]			X	X[P]				X	X[P]			X
Pharmacogenomics (PGx) – (Optional)[20, 24]		X[P]												
Study Drug injection[21]		X		X		X			X		X			
Local & Systemic Reactogenicity Assessment[22]		X		X		X			X		X			
Patient and Graft Survival														X

P = procedure should be completed prior to dosing * = Visit procedures may be performed by Home Health Care (HHC)

Table 1a: Plasma Viral Load Schedule

	Every Other Week								Monthly						
	Day 100*	Day 114*	Day 128*	Day 142*	Day 156*	Day 170*	Day 184	Day 198*	Day 230*	Day 260	Day 290*	Day 320*	Day 350*	Day 380*	Day 395
CMV Visit Window (days)	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+14/-5
CMV Window							Day 179-189	Day 193-203		Day 255-267					
Overlap with Regular Visit†							Days 179-185	Days 191-197		Days 260-267					Days 395-409
May draw with Visit:	Visit 7*						Visit 10	Visit 11*		Visit 12					Visit 13
CMV Plasma Viral Load Testing[16, 17, 24]	X	X	X	X	X	X	X[P]	X	X	X	X	X	X	X	X

* = Visit procedures may be performed by Home Health Care (HHC). Viral load blood draws may be combined with Visits 10, 11 12 & 13 at the investigator site when they are scheduled to coincide within each visit's windows .

† Days in Study Schedule when CMV and Regular Visit can be performed together per Protocol. The overlap used assumes the visits are done exactly on the specified visit day from Transplant. If +/- window is used for a dosing visit, the corresponding follow up visit should take place within the 14 days +/-3 from the date of the Study Drug dose. Visits 10 & 11 must be at least 7 days apart.

Tables 1 and 2 Footnotes:

1. Screening may be done from Day -14 up to Randomization, Day 30. Screening and Randomization can take place on the same day as long as Clinical Labs are drawn and results are available on the day of Randomization. If Screening is done > 3 days prior to Randomization, Clinical Labs, urinalysis and urine protein: creatinine ratio must be repeated and available prior to Randomization. Subjects may be rescreened due to rescheduling of transplant surgery provided the screening procedures are repeated and fall within the -14 day to + 30-day window relative to the Day of Transplant. First study drug dosing must take place within 24 hours of Randomization.
2. The date of transplant (day of skin closure) defines Day 0 and all visit days are relative to Day 0.
3. Subjects are to receive prophylactic valganciclovir or ganciclovir starting within 10 days post transplant through the Day of Randomization to prevent CMV disease. (The subject can miss up to two doses of valganciclovir or ganciclovir during this time period for any reason). Valganciclovir or ganciclovir dose is to be given per the package insert. The subject will then continue to receive CMV-specific AVP until 100 days post transplant. Subjects can have CMV-specific AVP interrupted, dose adjusted or replaced by other CMV-specific AVP per standard of care after the Day Randomization if renal function is compromised, there are toxicities related to the administration of the AVP, or for any other medically indicated reason.
4. Informed consent must be obtained prior to the performance of any study-related procedure.
5. Subjects will be assigned a subject number for use throughout the study at the Screening Visit via the Interactive Response Technology (IRT) system.
6. The EQ-5D, Kidney Transplant Questionnaire (KTQ) and the SF-12 v2, should be completed by the subject prior to any other study assessments or visit procedures. Subjects should complete these assessments in the following order: EQ-5D first, KTQ second, SF-12 last. For all three patient-reported outcome measures, i.e. EQ-5D, KTQ, SF-12, the answers must come from the subject. If the subject is unable to fill out the questionnaire, the assessment should not be performed. If the subject is unable to answer an individual question, the rest of the questionnaire should still be completed.
7. Medical history must include demographics, (age, gender, race), diagnosis for renal failure, length of time on dialysis, history of prior kidney transplant, and diabetes.
8. A complete physical examination (PE) will be conducted at the Screening, Baseline and the Study Completion/Day 395 Visit (V13). At all other visits where a PE is performed (Visits 4, 6, 8, 10 and 12); symptom-directed physical examinations may be done. The evaluations conducted at each visit are to be performed by the Investigator or qualified medical personnel who routinely perform these evaluations in this patient population. Vital signs will be collected immediately prior to Study Drug injection, at 15 minutes and 60 minutes post Study Drug injection. Vital signs include blood pressure, pulse rate, respiratory rate and temperature. Height will be collected at the Screening Visit only. Weight will be collected at V1, V2 and at Study Completion/Day 395 (Visit 13). If Screening is done > 3 days prior to Randomization, the PE must be repeated at Randomization.
9. All concomitant medications and therapies administered from 14 days prior to transplant through the Study Completion Visit (Day 395/Visit 13) will be collected on the eCRF. Medications used for anesthesia during the transplant surgery will not be recorded.
10. Clinical laboratory samples will be drawn at Screening (Visit 1), before each Study Drug injection, at each follow-up time point for the injections, and at the last study visit. Clinical labs will be performed by a local laboratory and will include hematology, biochemistry, including a hepatic profile, urinalysis with microscopic evaluation and urine protein: creatinine ratio. Screening clinical labs may be re drawn once if initial results would preclude Randomization and the Investigator feels out of range results were transient. Results will be entered into the eCRF. Safety labs (hematology, biochemistry, hepatic profile, urine protein: creatinine ratio and urinalysis) drawn by Home Health Care for Investigator sites utilizing this service will be analyzed by the Central Laboratory.

11. For all females of childbearing potential, a urine pregnancy test will be performed at Screening, prior to each dose, at Visit 10, 12, and at the Study Completion/Day 395 Visit (Visit 13). All pregnancy tests will be done locally. For subjects who receive mycophenolate mofetil (MMF), additional pregnancy testing should be done in accordance with local requirements.
12. CMV serologies must have been performed within 8 weeks prior to transplant. If CMV serostatus is not available from this time period, CMV serostatus may be assessed at the Screening Visit with results available prior to Randomization.
13. AEs and SAEs will be collected from time of signing of informed consent through one year post Study Drug injection [Study Completion Day 395 Visit (Visit 13)]. AEs should be recorded as a change in medical status or medical history, from the time of signing of the informed consent until the first dose of study drug. SAEs from the time of signing the informed consent will be recorded on the SAE worksheet and reported per Section 5.5.6. AEs reported after the first dose will be reported on the AE eCRF. Note: The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.
14. Transplant information includes type of transplant (Living Related Donor, Living Unrelated Donor, or Deceased Donor).
15. Donor information includes donor demographics (age, gender, race), viral serologies (CMV [required], HBV, HCV, EBV, [if available]; and HCV PCR RNA [if available]), ABO blood group and HLA typing. Recipient information includes ABO blood group, HLA typing, HLA cross match at time of transplant (as determined by the site's standard method of determination), and viral serologies (CMV [required], HBV, HCV and EBV [if available], and HCV PCR RNA [if available]).
16. Plasma viral load by the central laboratory will be routinely monitored every other week (+/-3 days) from Day 100 through Day 200, then monthly (+/- 5 days) until end of study. Plasma viral load by central and local laboratory will also be assessed for cause in case of suspect CMV disease and at least once a week by Central lab from initiation of CMV-specific AVT until the course is completed. For cause CMV viral loads should be performed at a local lab approved by Astellas as Central lab viral load results may not be available in a timely manner to guide treatment decisions.
17. Plasma viral load assessment results performed by the local laboratory will be reported on the eCRF. Local CMV plasma viral load testing may be performed only at a local laboratory approved by the Sponsor.
18. A plasma sample will be drawn and sent to the central lab and results will be reported for CMV genotypic resistance when there is viremia without a reduction in viral load after two weeks of treatment with valganciclovir and/or ganciclovir, or when clinical signs and symptoms have not improved two weeks after initiating or increasing valganciclovir and/or ganciclovir for CMV viremia or disease or any time resistance to any CMV-specific AVT is suspected by the Investigator.
19. Immunogenicity laboratories include collection of blood for the gB antibody and pp65 T-cell assays. Samples should be drawn at Visits 2, 5, 6, 9, 10 and 13. Visits 2, 6 and 10 are Study Drug injection visits and blood sampling will be collected prior to the Study Drug injection. Samples for T-cell assays will not be collected if the Absolute Lymphocyte Count (ALC) is known to be $\leq$ 500 mm^3 by local or central laboratory measurement.
20. Subjects who consent to participate in the PGx sub study will have a whole blood sample collected during the Baseline Visit (Visit 2), after Randomization but prior to the first Study Drug injection.
21. A Study Drug injection should not be given if the subject 1) has been on an anticoagulant within 5 half-lives prior to the injection(Low dose anticoagulants that are used for prevention of deep vein thrombosis are allowed) or 2) has a Temperature $\geq$ 100.4° F or 38° C (per NCI Grade 1).
22. Local reactogenicity and symptoms of systemic reactogenicity will be evaluated one hour after each injection and then for seven days after each injection by subject reporting via diary. After injection in the clinic, the subject must be in direct view of the clinic staff for 15 minutes following each injection, then remain in the clinic area for an additional 45 minutes for evaluation of local and systemic reactogenicity. Vital signs, including temperature, pulse, respiration and blood pressure will be collected just prior to injection, 15 minutes post Study Drug injection and at one hour post Study Drug injection. Using the pre-injection vital signs as baseline, if a post Study Drug injection vital sign meets Grade 1-4 criteria per Appendix 5, they are to be repeated and confirmed within 5 minutes of the first assessment.

23. The Study Completion/Day 395 Visit (Visit 13) must occur on Day 395 up through +14 days (between Day 395 to 379). For a subject who prematurely withdraws from the study (discontinues treatment with no continued follow-up), the Study Completion Visit should be completed within 14 days of study withdrawal.
24. Specimen drawn and sent to the Central Laboratory.
25. If a Study Drug dose is missed, the 14 day follow up clinical laboratory samples for hematology, biochemistry, urinalysis and urine protein: creatinine ratio and hepatic profile should not be collected. Scheduled Immunogenicity Labs (Visit 5 & 9) must still be collected.

Table 2: Schedule of Assessments – Long-term Follow-up Period

Month	18	30	42	54	66
Year (relative to first Study Drug)	1.5	2.5	3.5	4.5	5.5
Window (months)	± 1	± 1.5	± 1.5	± 1.5	± 1.5
Mortality, including primary cause of death and date	X	X	X	X	X
Development of any new malignancies	X	X	X	X	X
Development of infection requiring hospitalization or resulting in death	X	X	X	X	X
Erythema and/or induration at sites of immunizations	X	X	X	X	X
Graft Survival	X	X	X	X	X
Creatinine*	X	X	X	X	X

Subjects will be contacted by telephone at 6 months after Day 395, then annually, for the next 4 years for long-term safety related to the DNA vaccine. Items are to be assessed by questionnaire and via retrospective chart review of available medical records.

During the long-term follow-up period, if an SAE is identified and deemed possibly or probably related to the study medication, an SAE report on the SAE worksheet must be sent to the sponsor per Section 5.5.6.

*Creatinine values will be recorded if they have been collected within 3 months prior to the follow-up telephone contact and are included in the subject's available medical records.

1 INTRODUCTION

1.1 Background

CMV is a member of the Herpesviridae family, double-stranded DNA viruses which become latent in host cells after acute infection. CMV infection is ubiquitous and evidence of sero-conversion has been found in all populations. CMV 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.

The morbidity and mortality associated with CMV infection is secondary to both the direct and the indirect effects of CMV. CMV 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.

The use of either prophylactic or preemptive anti-viral therapy (AVT) has led to a reduction of CMV disease, but late CMV disease, after therapy is discontinued remains a problem.

In addition to the direct effects of CMV infection (CMV disease) the indirect effects of CMV infection include allograft rejection, decreased graft and patient survival, and an increase in opportunistic infections [Fishman & Rubin, 2007]. The indirect effects may possibly result from alterations in the immune system after subclinical reactivation episodes or by expression of viral genes during latency [Boeckh & Geballe, 2011].

Vaccines designed to induce or enhance the adaptive immune response to CMV could reduce the risk of CMV disease, allograft rejection, graft and patient survival and opportunistic infections other than CMV. The control of CMV infection is associated with preserved CMV-specific cellular immune responses, including CD4+, CD8+, and natural killer (NK) T cells [Sylwester et al, 2005]. In addition, humoral responses have also been shown to be important in preventing viral dissemination [Griffiths et al 2011].

ASP0113 is a first-in-class vaccine that is designed for the prevention of CMV infection in SOT recipients through stimulation of both humoral and cell-mediated immune responses. It contains 2 plasmids which encode CMV glycoprotein B (gB) and tegument phosphoprotein 65 (pp65). gB is the major neutralizing target for antibodies stimulated by CMV in healthy humans [Britt et al, 1990]; pp65 is one of the proteins most frequently recognized by CD8 cells after a CMV infection in healthy humans [Kern et al, 2002; Gyulai et al, 2000; Wills et al, 1996]. ASP0113 has been studied in subjects undergoing hematopoietic cell transplant and warrants further study in the SOT population.

1.1.1 Non-clinical and Clinical Data

In mice, vaccination with ASP0113 leads to production of antibodies against gB and pp65 and a robust T-cell response to pp65. Plasmid numbers of ASP0113 are barely detectable at the injection site and are not associated with genomic DNA 2 months after vaccination.

Administration of ASP0113 as a single dose is well-tolerated and results in no demonstrable clinical signs of toxicity due to injection of vaccine. Repeat dose administration of ASP0113 in rabbits is well-tolerated, with no vaccine-related changes in clinical signs and symptoms. However, vaccination with ASP0113 did lead to a significant, but reversible, increase in creatine phosphokinase (CPK) and minimal to moderate inflammation of the muscle, skin and subcutis, that persisted to a slight degree in the recovery period. Based on these nonclinical animal studies, ASP0113 is not anticipated to present a toxicity risk in humans when delivered by intramuscular injection, and immunogenicity data suggest that vaccination can induce immune responses to human CMV. For a detailed summary of the preclinical studies please refer to the current Investigator's Brochure (IB) .

1.1.2 Clinical Data

To date, ASP0113 has been evaluated in a Phase 1 study in healthy volunteers and a Phase 2 study of matched related donor/recipient pairs and related or unrelated recipients undergoing allogeneic HCT for hematologic disorders.

1.1.3 Phase 1 (VCL-CB01-101) Results

The first clinical study of ASP0113 was a multicenter, randomized, open-label Phase 1 clinical study (VCL-CB01-101) designed to evaluate the safety and immunogenicity of ASP0113 in 44 healthy adult CMV-seropositive and CMV-seronegative volunteers at doses of either 1 mg or 5 mg (IM) administered on weeks 0, 2, and 8 in a dose escalation format and at a dose of 5 mg (IM) administered on days 0, 3, 7 and 28 (accelerated schedule)[Wloch et al, 2008].

Volunteers receiving the higher dose or accelerated vaccine schedule tended to experience more local reactogenicity, but the severity of the treatment-emergent adverse events (TEAEs) did not increase with increasing dose and a more compressed schedule. The incidence of local reactogenicity, predominantly injection site pain, was 62.5% for the lowest weekly dose group, 87.5% for the highest weekly dose group, and 100% for the accelerated schedule group. Several cutaneous TEAEs (4.2%) were considered related to ASP0113 by the Investigator and included erythema, rash and pruritus. One volunteer did experience a transient increase in CPK value greater than 5 x the upper limit of normal, but less than 10x normal.

Immune responses to the 2 immunogens encoded in the vaccine, gB and pp65, were assessed by the use of an indirect gB binding enzyme-linked immunosorbent assay (ELISA) for antibody responses to gB and a pp65 direct ex-vivo interferon gamma (IFN-γ)enzyme-linked immunosorbent spot (ELISPOT) assay for T-cell responses to pp65. At 16 weeks, antibody and cell responses were elicited in 38% and 50% of the CMV-seronegative volunteers administered 1 mg and 5 mg ASP0113, respectively. CMV-seropositive volunteers had increases in pp65 T-cell responses of 12.5% and 37.5% across all groups, but no increase in gB antibody levels were detected for CMV-seropositive volunteers.

1.1.4 Phase 2 (CB01-202) Results

The second clinical study of ASP0113 was a multicenter, randomized, double-blind Phase 2 clinical study designed to evaluate the efficacy, immunogenicity and safety of ASP0113 in donors and CMV-seropositive recipients undergoing 5 of 6 or 6 of 6 HLA-allele-matched allogeneic HCT for the treatment of hematologic disorders [Kharfan-Dabaja et al, 2012]. A total of 108 subjects were enrolled in the study, including 14 donor/recipient pairs, and received at least one dose of Study Drug [5 mg/mL (1 mL dose)] or placebo. Recruitment of donor/ recipient pairs was found to be impractical early in the study so that arm was discontinued; the results are not discussed here. The intent-to-treat (ITT) and per protocol (PP) populations comprise 80 and 74 transplant recipients, respectively. Recipients received injections at approximately Days -5 to -3, 21 to 42 (one injection in this window, health permitting), on Day 84, and on Day 196 relative to transplantation. Results discussed below are for the PP population.

The primary efficacy endpoint of the study was the occurrence of clinically significant CMV viremia, defined as detection of CMV viremia that resulted in the initiation of CMV-specific antiviral therapy during the first year of transplant. The clinical decision to treat at the sites was based on the most current local or central CMV assay results. CMV-specific antiviral therapy was initiated for a lower percentage of recipient subjects in the ASP0113 group (47%) than in the placebo group (61.8%), but the difference was not statistically significant (p=0.145, Cochran-Mantel-Haenszel test stratified by site). The PP population was modified for this analysis to exclude two subjects who received CMV-specific AVT because of false positive results from the local viral load assay.

When the occurrence of CMV viremia, as defined as $\geq$ 500 copies/mL by a laboratory developed test (LDT) based upon the LightCycler® polymerase chain reaction (PCR), was evaluated in a central laboratory, the rate was lower in the ASP0113 group (33%) than in the placebo group (62%) and was statistically significant (p=0.008, Cochran-Mantel-Haenszel test stratified by site). Exploratory endpoints also demonstrated a delay in time to initial viremia (p=0.003), number of CMV infection episodes (p=0.017) and duration of viremia when normalized as percentage of time on study (p=0.042).

Table 3: Viral Load Endpoints after 12-Month Follow-up in the CB01-202 Study – Per Protocol Population

		ASP0113 (n=40)	Placebo (n=34)	P value
Occurrence of CMV infection (≥ 500 copies/mL)		13 (33%)	21 (62%)	0.008†
Time to initial viremia (days)	Median	> 365	109.5	0.003ǂ
Number of CMV infection episodes	0	27 (68%)	13 (38%)	0.017§
	1	8 (20%)	14 (41%)	
	2	4 (10%)	3 (9%)	
	3	1 (3%)	3 (9%)	
	4	0	1 (3%)	
Duration of viremia (days)	Mean	10.6 (0-68)	19.4 (0-181)	0.071§
Duration of viremia (normalized as % of time on study)	Mean	4.9 (0-63)	7.6 (0-49)	0.042§
Viral load area under the curve (copies mL*days)	Mean	66,238	127,875	0.069§
	Median	0	37,000	
	Range	0-1 x 10^6	0-2 x 10^6	
Peak viral load (copies/mL)	Mean	2838	8971	0.061§
	Median	0	3250	
	Range	0-29,500	0-145,000	

All results are based on LightCycler® PCR assay for CMV (Roche Molecular Systems) using analyte specific reagents performed at the [redacted].
P value was computed by: †Cochran-Mantel-Haenszel test stratified by site, ǂlog rank test stratified by site or §Wilcoxon rank sum.

In a post hoc analysis, the rate of the following clinical endpoints were numerically reduced, but were not statistically significant. Acute Graft vs. Host Disease (aGVHD) (grade 3-4) occurred less frequently in the ASP0113 group (5.0%) than in the placebo group (14.7%) (p=0.2364); chronic Graft vs. Host Disease (cGVHD) (high risk) occurred less frequently in the ASP0113 group (10.0%) than in the placebo group (20.6%) (p=0.3259. In addition, the incidence rate of a composite endpoint of CMV EOD, mortality (overall), aGVHD (grade 3-4), and cGVHD (high risk) was lower in the ASP0113 group (32.5%) than in the placebo group (52.9%), although the difference was not statistically significant (p=0.1719).

Immune responses to the two immunogens, gB and pp65, encoded in the vaccine were assessed by two immunoassays: 1) a gB-specific IgG-binding ELISA; and 2) an ex vivo pp65-specific IFN-gamma ELISPOT [Kharfan-Dabaja et al, 2012]. T-cell responses to CMV pp65 and gB as well as gB-specific serum antibody levels were similar in the ASP0113 and placebo recipients prior to conditioning therapy and transplant. The CMV pp65 T-cell responses were numerically enhanced in the ASP0113 group relative to the placebo group at all post-transplant times evaluated; the differences in the responses were statistically significant at Day 84 (p=0.036 Wilcoxon rank sum test). Please refer to the Investigators' Brochure regarding other post-hoc analyses of the immunogenicity data.

The geometric mean gB-antibody levels in recipients in the ASP0113 group compared with recipients in the placebo group showed a trend towards significance at the fourth injection

(p=0.064, Wilcoxon rank sum test) and reached significance by day 365 (p=0.009, Wilcoxon rank sum test). Although the geometric mean gB antibody levels were higher for the ASP0113 recipients at all time points evaluated, the repeated measurement ANOVA using $\log_{10}$ transformed data from days 56 to 365 did not show a significant difference between the longitudinal gB antibody responses (p=0.749).

The incidence of local reactogenicity was higher in the ASP0113 group than in the placebo group (22.9% and 10.9%, respectively), primarily due to injection site pain. Fatalities were reported for 20.8% recipients in the ASP0113 group and 32.6% recipients in the placebo group during the 1-year study follow-up. No recipient died due to Study Drug-related AEs. No subject experienced CPK elevation in this study. One subject in the ASP0113 arm discontinued the study due to a serious allergic reaction that was considered by the Investigator to be possibly related to ASP0113 (subject number [redacted]). [redacted]

1.2 Summary of Key Safety Information for Study Drugs

ASP0113 in nonclinical studies was in general well-tolerated. Nonclinical studies demonstrated that the risk of integration of injected DNA into the host's genome is negligible per FDA regulatory guidance and induction of autoimmunity is unlikely. No systemic organ toxicity was noted. There was no local reactogenicity reported, but in the highest dose groups in a repeated-dose toxicity study in rabbits, there was histological evidence of inflammation in the muscles injected with vaccine and concurrent elevations in CPK.

One healthy volunteer had a transient elevation in CPK (> 5x normal but < 10x normal). Local (injection site) reactions including pain, induration, erythema, pruritus, discomfort and swelling were reported more frequently in the higher dosing group and more accelerated schedule with ASP0113 in healthy volunteers and in the ASP0113 treated group when compared to the placebo group. The only discontinuation due to an SAE that was possibly related to ASP0113 was the transplant recipient who was previously discussed in section 1.1.4.

1.3 Risk-Benefit Assessment

Despite currently licensed CMV-specific antiviral therapies, CMV disease continues to cause significant morbidity and mortality in solid organ transplant recipients and CMV infection may be associated with multiple other clinical outcomes including allograft rejection, decreased graft and patient survival, and an increase in opportunistic infections [Fishman & Rubin, 2007]. In addition, the treatments and associated toxicities can incur significant healthcare costs. Prophylactic valganciclovir is approved for 200 days after transplant in the United States and 100-200 days in Europe and Canada. From 100-200 days, subjects will have a viral load

assessed by central laboratory and treated preemptively per the standard of care at the institution.

ASP0113 appeared to show efficacy in a single Phase 2 trial over multiple secondary endpoints [Kharfan-Dabaja et al, 2012]. The incidence of local reactogenicity may be greater with ASP0113 than placebo. In addition, while there were CPK elevations at the highest dose level in toxicity studies in rabbits, significant damage to the muscle, as determined by CPK elevations greater than 10 x upper limit of normal, has not been observed in humans. One SAE (hypersensitivity/allergic reaction) leading to discontinuation responded well to medical treatment and was deemed not life-threatening. False positive results in the assessment of CMV viral load can occur in subjects receiving ASP0113 with the use of PCR assays that utilize primers targeted at gB and pp65. Such false positive results, if unrecognized, can lead to misdiagnosis and unnecessary initiation of antiviral therapy. It is unknown if false positive results can occur with the pp65 antigenemia assay.

Given the morbidity and mortality associated with CMV infection and treatment, signals of possible efficacy in a phase 2 trial in HCT recipients, ASP0113 warrants further investigation in the prevention of CMV infection in patients receiving a solid organ transplant.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

The objectives of this study are:

- To evaluate the efficacy of ASP0113 compared to placebo in reducing the incidence of CMV viremia (defined as plasma viral load ≥ 1000 IU/mL by central laboratory assay) through one year post first Study Drug injection in CMV-seronegative subjects receiving a kidney from a CMV-seropositive donor.
- To evaluate the safety of ASP0113 in CMV-seronegative subjects receiving a kidney from a CMV-seropositive donor.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a randomized, double-blind, placebo-controlled trial which will enroll 140 CMV-seronegative recipients of kidney transplant from a CMV-seropositive donor at 80 clinical sites. Subjects will be randomized at Day 30 ±3, in relation to the day of transplant, in a 1:1 ratio to ASP0113 or placebo, and stratified by use of anti-thymocyte globulin (ATG) prior to Randomization and by receipt of a kidney from a living or deceased donor. The active compound will be a vaccine (ASP0113) which contains two plasmids encoding gB and pp65 each at 2.5 mg/mL, formulated with CRL1005 poloxamer and benzalkonium chloride (BAK).

The placebo control will be phosphate-buffered saline (PBS). Subjects will receive either 5 doses of ASP0113 or placebo on Days 30 ± 3, 60 ± 5, 90 ± 5, 120 ± 5 and 180 ± 5 in relation to the day of transplant (Day 0).

Injections should be administered only when there is no medical contraindication to an intramuscular (IM) injection. Syringes will be masked prior to dosing to blind the subjects and all other personnel who need to remain blinded to the treatment assignment (i.e., site staff other than pharmacy personnel and staff designated to administer Study Drug injections).

Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) through the day of Randomization to prevent CMV disease. (The subject can miss up to two valganciclovir or ganciclovir doses during this time period for any reason). Subjects will then continue to receive CMV specific CMV AVP with valganciclovir or ganciclovir (dose per package insert) to prevent CMV disease until 100 days post transplant. Subjects can have valganciclovir or ganciclovir interrupted, dose adjusted or replaced by other CMV-specific AVP per standard of care after the day of Randomization if renal function is compromised, there are toxicities related to the administration of the AVP or for any other medically indicated reason. In all subjects, plasma will be collected for central laboratory CMV viral load testing every two weeks from Day 100 through Day 200, then monthly through last Study visit Day 395.

In cases where CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected from the first Study Drug injection through Day 395, a local CMV viral load sample will be collected at the time of the first CMV symptom recognition.

Through Day 395, CMV-specific AVT should be initiated for CMV disease and can be initiated for CMV viremia based on the central or local laboratory results and standard of care at each institution. If CMV- specific AVT is initiated, a central CMV viral load will be obtained at a minimum of weekly from the time CMV- specific AVT is initiated until discontinuation. For cause CMV viral loads should be performed at a local lab approved by Astellas as Central lab viral load results will not be available in a timely manner to guide treatment decisions.

In addition, every time a sample is collected for a local CMV viral load, a plasma sample should also be collected and sent to the central laboratory for CMV viral load testing.

As one of the plasmids of the ASP0113 vaccine codes for the pp65 antigen, the theoretical possibility of interference with the pp65 antigenemia assay has been raised. At present, there are no data to suggest that such an interference occurs. However, to ensure subject safety and study integrity, sites that use pp65 antigen as their local methodology for the detection of CMV infection must adhere to the procedures defined below as a condition of participation in the trial:

- The local pp65 antigenemia results must be entered into the eCRF database within 72 hours (or next business day) of receipt to facilitate in-time monitoring of results.
- The Medical Monitor must be called within 48 hours (or next business day) if the pp65 antigenemia test is positive and the central laboratory PCR viral load result is negative.

- Both the pp65 antigenemia and the central laboratory test must be repeated within 48 hours of receipt of results, if the local pp65 antigenemia result is positive, the central laboratory PCR viral load result is negative and the subject is treated with CMV-specific AVT . Further treatment decisions are to be discussed with the Medical Monitor.

The plasmids in the Study Drug may interfere with certain PCR assays. If a PCR assay is used that amplifies the genes UL55/gB or UL83/pp65, this could result in either a false positive viral load or unblinding of the study subject.

Sites that are determined to have an unacceptable assay in their local lab but are able to determine a Sponsor- deemed acceptable work practice flow for utilizing another acceptable local assay or methodology will be allowed to participate in the trial. Note**:** Local CMV plasma viral load testing may be performed only at a local laboratory approved by the Sponsor.

Subjects will be followed for one year after first Study Drug injection (Primary Study completion/Day 395) for CMV viremia, CMV syndrome, CMV tissue-invasive disease, CMV-specific AVT, graft survival fand subject survival.

Subjects will be followed for one year after the first Study Drug injection for resistance to valganciclovir or ganciclovir. Viral resistance will be assessed by a Central lab when there is no reduction in viral load two weeks after initiating valganciclovir/ganciclovir, when there is no improvement in clinical signs and symptoms two weeks after initiating valganciclovir/ganciclovir or any time resistance to any CMV-specific AVT is suspected by the Investigator.

Immunogenicity to pp65 and gB will be assessed prior to Dose 1, two weeks after Dose 2, prior to Dose 3, two weeks after Dose 4, prior to Dose 5 and at the last study visit.

Subjects will be evaluated for local and systemic reactogenicity 15 minutes and one hour after each Study Drug injection and for 7 days by subject reporting via diary after each Study Drug injection.

Subjects will be contacted by telephone at 6 months after Day 395, then annually for the next 4 years to evaluate long-term safety related to the DNA vaccine. Items to be assessed by questionnaire and available patient records include mortality, development of any new malignancies, development of infection requiring hospitalization or resulting in death, graft survival, creatinine, and erythema and/or induration at the injection sites (see Appendix 17).

All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post Study Drug injection. AEs occurring from signing of informed consent until just prior to the first dose of Study Drug, should be reported as a change in medical status or medical history. SAEs from the time of signing the informed consent will be recorded on the SAE worksheet and reported per Section 5.5.6.AEs reported after the first dose will be reported on the AE eCRF. The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.

An independent Data Monitoring Committee (DMC) will be chartered to oversee the safety of subjects and review of the futility analysis. An Adjudication Committee (AC) will be

chartered to adjudicate all cases of CMV syndrome, CMV tissue-invasive disease and CMV-specific antiviral therapy.

2.2.2 Dose Rationale

Efficacy and safety data were collected from normal healthy subjects in a Phase 1 trial as well as HCT recipients in a Phase 2 clinical trial (VCL-CB01-101 and CB01-202, respectively). The dose used in the Phase 2 study was 1 mL of 5 mg/mL and 4 doses were given over approximately a 6 month time period. The dose and dose schedule appeared to be well tolerated.

In the current study, five doses of 1 mL of 5 mg/mL of Study Drug or Placebo are planned. The first two doses will be given during the CMV-specific prophylactic therapy to prime the immune response. The third dose will be given at 90 days post transplant to boost the immune response at the time that CMV-specific prophylaxis is discontinued. The last two doses will be given on Days 120 and 180 to coincide with late onset CMV disease.

2.3 Endpoints

2.3.1 Primary Efficacy Endpoints

Incidence of CMV viremia (defined as plasma viral load of ≥ 1000 IU/mL by central assay) through one year post first Study Drug injection.

2.3.2 Secondary Efficacy Endpoints

Incidence of :

- Adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- CMV viremia (defined as plasma viral load ≥ the lower limit of quantification [LLOQ]) by central assay through one year post first Study Drug injection.
- Adjudicated CMV-specific antiviral therapy for the treatment of CMV viremia or disease through one year post first Study Drug injection.
- Graft survival through one year post first Study Drug injection.
- Subject survival through one year post first Study Drug injection.

2.3.3 Exploratory Efficacy Endpoints

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ 1000 IU/mL by central assay) through one year post study first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.

- Number of episodes of CMV viral load of ≥ 1000 IU/mL by central assay through one year post first Study Drug injection.
- Peak CMV viral load and area under the curve (AUC) through one year post first Study Drug injection.
- Viral load area under the curve (AUC), as a measure of "cumulative viral load" through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of viral resistance to ganciclovir or valganciclovir through one year post first Study Drug injection as determined by a central laboratory assay.
- Incidence of biopsy-proven (T or B cell) rejection (BPAR)(Banff 2007 Grade ≥ 1) through one year post first Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at the last study visit calculated using the 4 variable MDRD formula.
- Incidence of clinically treated acute graft rejection through one year post first Study Drug injection.
- Patient-reported outcomes through one year post first Study Drug injection.
    - EuroQol-5 dimensions 5 levels (EQ-5D)
    - Kidney Transplant Questionnaire (KTQ)
    - Short Form Health Survey version 2 (SF-12v2)
- Healthcare resource utilization through one year post first Study Drug injection.
    - Resource use will be collected including the following: hospitalizations recorded as number of days in the Intensive Care Unit, Step-down Unit, and general medical ward (including emergency room visits greater than 24 hours), also non - protocol -related physician visits and emergency room visits of less than 24 hours.

2.3.4 Immunogenicity Variables

- T-cell responses to pp65 through one year post first Study Drug injection.
- gB-specific antibody levels through one year post first Study Drug injection.

2.3.5 Safety Variables

- Vital signs.
- Adverse Events using the NCI-CTCAE v. 4.03 grading scale.
- Local reactogenicity signs and symptoms using both the NCI-CTCAE v. 4.03 grading scale and the protocol-specified reactogenicity scale.
- Systemic reactogenicity signs and symptoms using both the NCI-CTCAE v. 4.03 grading scale and the protocol-specified reactogenicity scale.
- Clinical laboratory assessments as defined in appendices.
- Physical examination.

3 STUDY POPULATION

3.1 Selection of Study Population

This study will randomize kidney transplant recipients who are at least 18 years of age or of legal age of consent, whichever is greater, and are CMV-seronegative and have received a kidney from a CMV-seropositive donor.

Subjects will be enrolled in the trial based on negative CMV serostatus as confirmed by a local laboratory from 8 weeks prior to transplant through day of transplantation. If CMV serostatus is not available from this time period, CMV serostatus may be assessed at the Screening Visit and results must be available at the time of Randomization.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability (HIPAA) Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-specific procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is willing to comply with the protocol.
3. Subject is ≥ 18 years of age or the legal age of consent (whichever is greater).
4. Subject is CMV-seronegative at time of transplant and has received a kidney allograft from a CMV-seropositive living or deceased donor. CMV serostatus of the recipient can be determined from 8 weeks prior to transplant, by local laboratory, through day of transplantation. If CMV serostatus is not available from this time period, CMV serostatus may be assessed at the Screening Visit, by local laboratory, with results available prior to Randomization.
5. Subject started valganciclovir or ganciclovir within 10 days of transplant and has received it through Randomization per regulatory label (package insert).
6. Female subject must be either:
   - Of non- child-bearing potential:
     - post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
     - documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening).
   - Or, if of childbearing potential:
     - must have a negative urine pregnancy test at Screening, and
     - if heterosexually active, must use two forms of birth control* (at least one of which must be a barrier method) starting at Screening and during the Primary Study Period.

7. Female subject must not be breastfeeding at Screening and during the Primary Study Period.
8. Female subject must not donate ova starting at Screening and during the Primary Study Period.
9. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control* (one of which must be a barrier method) starting at Screening and during the Primary Study Period.

   * Acceptable forms include:
   - Established use of oral, injected or implanted hormonal methods of contraception.
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
   - Partner male sterilization (i.e., vasectomy)
10. Male subject must not donate sperm starting at Screening and during the Primary Study Period.
11. Subject agrees not to participate in another interventional drug study while on treatment.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject is planned to undergo a course of CMV-specific prophylactic therapy with antiviral drugs with a duration of greater than 100 days.
2. Subject has received from one month prior to transplant or is planning to receive CMV immunoglobulin.
3. Subject has had CMV viremia or CMV disease from time of transplant until time of Randomization.
4. Subject has received, at any time, an organ transplant other than a kidney. (Dual allocation of a kidney is allowed).
5. Subject requires dialysis on the day of Randomization.
6. Recipient or donor is known to be positive for human immunodeficiency virus (HIV), hepatitis B surface antigen, or hepatitis B core IgM or IgG antibody.
7. Subject is known to have latent or active tuberculosis which has not been adequately treated.
8. Subject required desensitization for ABO blood type incompatibility or a positive T or B cell crossmatch.

9. Subject has received any of the following substances or treatments:
    a. Investigational therapy within 28 days or 5 half lives whichever is longer, prior to Transplantation, or subject is scheduled to receive investigational research products through one year after Randomization.
    b. Alemtuzumab within 90 days prior to Randomization or is scheduled to receive alemtuzumab any time through one year post Randomization.
    c. Rituximab within 120 days prior to Randomization or is scheduled to receive rituximab any time through one year post Randomization.
    d. Eculizumab or bortezomib from the Day of Transplantation through the Day of Randomization or is scheduled to receive eculizumab or bortezomib any time through one year post Randomization.
    e. IVIG and/or plasmapheresis from Day of Transplant through Day of Randomization.
    f. Live attenuated vaccines within one month (30 days) prior to the first dose of Study Drug or is scheduled to receive live attenuated vaccines within one month of any Study Drug injection.
    g. Subunit or killed vaccines within 14 days prior to the first dose of Study Drug or is scheduled to receive subunit or killed vaccines within 14 days of any Study Drug injection.
    h. Administration of a CMV vaccine, including any prior exposure to ASP0113.
    i. Subject has received the following anti-viral therapies or it is planned for them to receive the AVT for prophylaxis of viral infections in excess of the following doses from time of transplant through Randomization:
        - *Aciclovir:* 1600 mg orally (total daily dose), or 500 mg/m^2/dose IV (total daily dose)
        - *Valaciclovir:* 1000 mg orally (total daily dose)
        - *Famciclovir:* 500 mg orally (total daily dose)
10. Subject has received any anticoagulants including, but not limited to, vitamin K antagonists, heparin or its derivatives, low molecular weight heparin, factor X inhibitors, or thrombin inhibitors within 5 half-lives prior to randomization or is expected to use anticoagulants within 5 half-lives prior to any Study Drug injection. Low dose anticoagulants that are used for prevention of deep vein thrombosis and antiplatelet agents are allowed.
11. Subject has any contraindication to or cannot be dosed with valganciclovir or ganciclovir per package insert on the Day of Randomization for any reason.
12. Subject has, or is expected to have during the Primary Study Period, a contraindication to an intramuscular injection.
13. Subject, within 3 days prior to Randomization, has an AST or ALT greater than 3 x ULN or total bilirubin greater than 2 x ULN unless secondary to suspected Gilbert's disease.

14. Subject has a current malignancy or a recent history of malignancy (within the past 5 years prior to Screening) except non-metastatic basal or squamous cell carcinoma of the skin that has been treated successfully or cancer *in situ* of the cervix uteri that has been successfully treated by local therapy.
15. Subject is being treated for an active infection at the time of Randomization.
16. Subject has any condition or an unstable medical or psychiatric condition, including a history of illicit drug(s) or alcohol abuse that the Investigator believes will place the subject at unacceptable risk or interfere with compliance to protocol requirements.
17. Subject has any other condition which, in the opinion of the Investigator, precludes the subject's participation in the trial.
18. Subject has known allergies or previous adverse reactions to ganciclovir or valganciclovir.
19. Subject has had an allergic reaction to any component of the vaccine, or to amino-glycosides, as kanamycin is used during the manufacturing process of the vaccine.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Vaccine(s)

ASP0113 contains 2 closed circular plasmid macromolecules. The plasmids are purified from cellular components and formulated with CRL1005 poloxamer and benzalkonium chloride (BAK), a cationic surfactant, in phosphate-buffered saline (PBS). The combination of CRL1005 and BAK produces a thermodynamically stable self assembled particulate system with a defined particle size, surface charge and stability profile at room temperature. BAK is used to control and maintain the particle size distribution of the formulation.

ASP0113 will be supplied by the Sponsor as a frozen solution in single dose 2-mL vials containing 1.3 mL of 5 mg/mL ASP0113. ASP0113 is packaged in a cardboard secondary container.

ASP0113 is a milky white suspension at room temperature, and clear at temperatures below the cloud point of CRL1005 (4°C-7°C).

ASP0113 should be stored frozen at -25^{o}C ± 10^{o}C.

Detailed instructions for the preparation and administration of ASP0113 will be provided in the Pharmacy Manual.

4.1.2 Placebo

Placebo will be supplied by the Sponsor in 2-mL vials containing phosphate-buffered saline. It is a clear colorless liquid. Placebo will be stored frozen at -25°C ± 10°C. Detailed instructions for the preparation and administration of placebo will be provided in the Pharmacy Manual.

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at APGD-AUST or Sponsor's designee in accordance with APGD-AUST or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each carton and vial will bear a label conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

In the European Union, a qualified person of Astellas Pharma Europe B.V. (APEBV) or Sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

The study centers will be provided cartons each containing 6 vials of ASP0113 or placebo (vehicle). ASP0113 and Placebo should be stored in the original carton. The vials should be stored at -25°C ± 10°C until the day of dosing.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that Study Drug deliveries from the Sponsor are received by the investigator/or designee, and

- that such deliveries are recorded,
- that Study Drug is handled and stored according to labeled storage conditions,
- that Study Drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- that any unused Study Drug is returned to the Sponsor.

Drug inventory and accountability records for the Study Drugs will be kept by the investigator/or designee. Study Drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply Study Drugs to any persons except the eligible subjects in this study in accordance with the protocol.

- The investigator or designee will keep the Study Drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A Study Drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return Study Drug to the Sponsor or designee at the end of the study or upon expiration.
- Used or unused Study Drug should be returned to the depot for destruction unless prohibited by local policy. In this instance, Study Drug may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted by the Sponsor or representative. Should this occur, a copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor. Upon destruction, a copy of the certificate of destruction must be provided for the Sponsor files and site drug accountability records.

4.4 Blinding

This is a double blind study. Subjects will be randomized to receive ASP0113 or placebo in a double-blind fashion such that the investigator, Sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT).

4.4.1 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study medication blind will be maintained by the IRT system vendor.

The Data Monitoring Committee (DMC) will be provided with access to the dosing assignment for periodic review of the unblinded data as documented in the DMC Charter.

4.4.2 Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will

be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the investigator or other persons designated as sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Unblinding of the study medication should only be considered for subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study medication.

4.5 Assignment and Allocation

At the Screening Visit, after the Informed Consent Form (ICF) has been signed, site staff will access the IRT system, enter the subject's required information, and the subject will receive a subject number assignment through the IRT for use throughout the study.

Randomization will be performed via Interactive Response Technology (IRT). Prior to the initiation of the study treatment, the site staff will contact/access the IRT system in order to determine the randomly assigned treatment. Specific procedures for randomization through the IRT system are contained in the study procedures manual.

Subjects who subsequently meet the inclusion/exclusion criteria will be randomly assigned to receive either ASP0113 or placebo. The randomization to treatment will be stratified by the use of anti-thymocyte globulin and by receipt of a kidney from a living or deceased donor.

The IRT vendor will generate the randomization schedule. To obtain the randomized treatment assignment for a subject, the pharmacist or designee will utilize an IRT system, which is available seven days a week, 24 hours a day.

Randomization is to be done after the completion of the Screening period, and at least 30 days ± 3 days after transplant day (Day 0). After submitting required information about the eligible subject, the drug kit number assignment will be provided.

Study Drug assignment will remain blinded to all site staff except the pharmacist, designated staff and the unblinded administrator.

If a subject is randomized but does not receive Study Drug, the kit number will not be used again. In this instance, the treatment assignment should only be known by the pharmacist and designated staff (i.e., the blind must be maintained as it is with all other subjects).

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

One (1) mL of 5 mg/mL ASP0113 or placebo will be administered to the subjects at the clinical site via injection in the deltoid muscle, alternating sides with each dose, if possible. Preparation of Study Drug will be described in the Pharmacy Manual for the study. The syringes will be masked as described in the Pharmacy Manual to maintain the study blind.

5.1.1 Dose/Dose Regimen and Administration Period

Doses will be given at the following time points:

- Dose 1 at Day 30 ± 3 days, post transplant.
- Dose 2 at Day 60 (± 5 days)
- Dose 3 at Day 90 (± 5 days)
- Dose 4 at Day 120 (± 5 days)
- Dose 5 at Day 180 (± 5 days)

An injection should not be given if, 1) the subject has been on an anticoagulant within 5 half-lives prior to the injection or there is any other contraindication to an intramuscular injection or 2) has a Temperature ≥ 100.4° F or 38° C (per NCI Grade 1.) Low dose anticoagulants that are used for prevention of deep vein thrombosis are allowed. Immunosuppressive agents used to prevent rejection should be given according to the standard of care at the center and taking note of the list of prohibited medication.

5.1.2 Increase or Reduction in Dose of the Study Drug

Dose increases or decreases are not allowed. If a dose is missed, the subject should continue on the same schedule of study drug injections and the same schedule of assessments except for the Day 14 follow up visit for the missed dose; clinical labs for hematology, biochemistry and hepatic profile should not be collected. Scheduled Immunogenicity Labs (Visit 5 & 9) must still be collected.

5.1.3 CMV Prophylactic Therapy

Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) through Randomization to prevent CMV disease. (The subject can miss up to two valganciclovir or ganciclovir doses during this time period for any reason). After Randomization, subjects will then receive CMV-specific AVP until 100 days post transplant. Subjects can have CMV-specific AVP interrupted, dose adjusted or replaced by other CMV-specific AVP per standard of care after the day of Randomization, if renal function is compromised,there are toxicities related to the administration of the AVP or for any other medically indicated reason.Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

5.1.3.1 Viral Prophylaxis

Viral prophylaxis for infection other than CMV should be administered according to standard institutional protocols. Prophylactic use of aciclovir (acyclovir), valaciclovir (valacyclovir), or famciclovir should not exceed the following doses following transplant (Day 0) through one year post Study Drug injection (Day 395/Visit 13) [Kumar & Humar, 2011; Tomblyn et al, 2009].

Aciclovir: 1600 mg orally (total daily dose), or 500 mg/ m^2/dose IV (total daily dose).

Valaciclovir: 1000 mg PO (total daily dose).

Famciclovir: 500 mg PO (total daily dose).

These doses may be exceeded if necessary to treat active infections post first Study Drug injection.

5.1.3.2 *Pneumocystis jiroveci* Pneumonia Prophylaxis

Pneumocystis jiroveci pneumonia prophylaxis must be initiated for all study participants according to the site's standard practice for kidney transplant recipients and applied uniformly to all enrolled subjects. Dose may be adjusted or therapy interrupted for renal dysfunction, adverse events related to the administration of the therapy or for other clinically indicated reasons. If there is no prophylactic Pneumocystis protocol, the investigator must decide on appropriate *Pneumocystis jiroveci* pneumonia prophylaxis.

5.1.3.3 Prohibited Concomitant Medication

- Investigational research products through completion of Day 395 visit (Visit 13).
- Planned alemtuzumab and, anti-CD20 antibodies (including rituximab) eculizumab or bortezomib are not allowed from the Day of Randomization through the Primary Study Period (Day 395). These treatments may be given after the Day of Randomization if clinically indicated.

Prophylactic use of CMV immunoglobulin.

- Live attenuated vaccines within one month (30 days) prior to each Study Drug injection.
- Subunit or killed vaccines within 14 days prior to any Study Drug injection.
- Anticoagulants, within 5 half-lives of Study Drug administration, including but not limited to vitamin K antagonists, heparin or its derivatives, low molecular weight heparin, factor X inhibitors, or thrombin inhibitors. Low dose anticoagulants that are used for prevention of deep vein thrombosis and antiplatelet agents are allowed.

5.1.3.4 Concomitant Medication (Drugs and Therapies)

All concomitant medications, immunosuppressive agents and therapies administered from 14 days prior to transplant through the Primary Treatment Period (Visit 13/Day 395) will be recorded at each study visit on the eCRF. Subjects should be instructed not to take any new

medications or change the dose and frequency of their ongoing medications throughout the study period without consulting the investigator.

Medications used for anesthesia purposes during the transplant will not be recorded.

5.1.4 Treatment Compliance

The dose and schedule of study product administered to each subject will be recorded on the appropriate form at every Study Drug administration visit. Reasons for partial administration (such as subject intolerance of injection or loss of Study Drug through human error) or omission of Study Drug will also be recorded. This information, plus vial accountability through the IRT system for Study Drug at every administration visit will be used to assess compliance with the treatment.

Treatment compliance should be monitored closely and deviation in compliance should be reported to the Sponsor.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The subject's age, gender, race and ethnicity will be recorded at the Screening Visit.

5.2.2 Medical History

A detailed medical history for each subject, including history of prior CMV, history of transfusion starting at one month prior to transplant, diagnosis for renal failure, length of time on dialysis, history of prior kidney transplant and diabetes, will be obtained at the Screening Visit. All relevant past and present conditions will be recorded for the main body systems, as well as prior surgical procedures. Typical events related to post operative recovery from the current transplant that occur prior to consent for this trial will be listed as medical history. Any untoward medical events that occur during the Screening period (prior to Study Drug administration) will be captured as medical history in the eCRF.

5.2.3 Transplant Information

Type of transplant

Living Related Donor

Living Unrelated Donor

Deceased Donor

5.2.4 Donor Information

Demographics, (age, gender, race)

Viral Serologies; CMV (required), HBV, HCV, EBV (if available) and HCV PCR RNA, (if available)

ABO blood group

HLA typing

5.2.5 Recipient Information

ABO blood group

HLA typing

HLA cross match at time of transplant (as determined by the site's standard method of determination)

Viral Serologies CMV (required), HBV, HCV, EBV (if available), and HCV PCR RNA, (if available)

5.3 Efficacy and Immunogenicity Assessments

5.3.1 Primary Efficacy Assessment

CMV Plasma Viral Load as assessed by a central assay.

Central viral load will be assessed according to Table 1a (Schedule of Assessments), any time a measurement of a viral load is clinically indicated, during CMV anti-viral therapy and any time a local CMV viral load is collected.

5.3.2 Secondary Efficacy Assessments

- Adjudicated CMV disease: CMV syndrome and CMV Tissue Invasive Disease as defined in Appendix 7
- CMV Plasma Viral Load by Central Assay
- Adjudicated CMV-specific AVT for CMV viremia or CMV disease

Initiation of AVT with activity against CMV will be adjudicated by an Adjudication Committee as set forth in the Adjudication Charter.

- Graft Survival

Graft survival is defined as any subject that does not fit the definition of graft loss as follows: graft loss is defined as subject death; re-transplant; nephrectomy; or return to permanent dialysis (i.e., for > 30 days) at Study Month 13,/Day 395 and 6 months after Day 395 then, annually for the next 4 years.

- Subject Survival

Subject survival is any subject that is known to be alive at Study Month 13/Day 395. For the Long Term Follow Up period, patient survival is any subject that is known to be alive at the conclusion of the Long Term Follow-Up period.

5.3.3 Exploratory Efficacy Assessments

- Opportunistic infections as defined in Appendix 8

- CMV Plasma Viral Load by central assay
- CMV disease: CMV syndrome and CMV Tissue Invasive Disease as defined in Appendix 7
- Genotypic resistance to valganciclovir and ganciclovir
- Biopsy Proven Acute Rejection (BPAR) as defined in Appendix 6
- eGFR at the last study visit
- Clinically treated acute graft rejection

5.3.3.1 Immunogenicity

An indicator of immunogenicity elicited by the vaccine is predicted to be an increase in gB-specific antibody levels and the T-cell response to pp65 protein over time compared with the placebo group.

Two immunogenicity assessments will be performed:

1. T-cell response to viral protein pp65 using intracellular cytokine staining (ICS).
2. Antibody response to gB antigen using an ELISA-based platform.

Assessments will be done from peripheral blood mononuclear cells (T-cells) or serum samples (antibody) isolated over the course of the trial. Time points of the assessments are as follows:

On Visits V2, V5, V6, V9 and V10 and V13:

- Samples for T-cell assays will not be collected if the Absolute Lymphocyte Count (ALC) is known to be $\leq$ 500 mm^3 by local or central laboratory measurement.
- If the visit coincides with a study drug administration, the sample will be drawn prior to injection.

Further details will be available in the Laboratory Manual.

5.3.4 Resource Utilization and Patient Reported Outcomes

Additional assessments include the following patient reported outcome measures and resource utilization.

- EuroQol (EQ-5D)
- Kidney Transplant Questionnaire (KTQ)
- Short Form Health Survey version 2 (SF-12v2)
- Health Economic Assessment (HEA)

The EQ-5D, Kidney Transplant Questionnaire (KTQ) and the SF-12 v2, should be completed by the subject prior to any other study assessments or visit procedures. Subjects should complete these assessments in the following order: EQ-5D first, KTQ second, SF-12 last. For all three patient-reported outcome measures, i.e., EQ-5D, KTQ, SF-12, the answers must come from the subject. If the subject is unable to fill out the questionnaire, the assessment should not be performed. If the subject is unable to answer an individual question, the rest of the questionnaire should still be completed. The questionnaires will be provided in the local language of the subject.

Health economic information will be collected for subjects through the Primary Study Period Completion/Day 395 Visit (Visit 13) (See Section 5.3.4.4).

5.3.4.1 EQ-5D

The EQ-5D is an international standardized non-disease specific (i.e. generic) instrument for describing and evaluating health status. It is a measure of health-related quality of life (QOL), capable of being expressed as a single index value and specifically designed to complement other health status measures. The questionnaire will be provided in the local language of the subject. The EQ-5D has 5 domains: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each domain has 3 response levels (e.g., 1=no problems, 2=some problems, 3=extreme problems). In addition, it has a visual analogue scale that elicits a self-rating by the respondent of his/her health status (see Appendix 13).

5.3.4.2 Kidney Transplant Questionnaire

The KTQ is a 25-item questionnaire that includes five domains or subscales, i.e., physical symptoms (based on six items), fatigue (based on five items), uncertainty/fear (based on four items), appearance (based on four items), and emotional (based on six items). A mean score ranging from 1 to 7 is reported for each of the five subscales, with higher scores representing better functioning, well-being, or fewer problems [Laupacis et al, 1993] (Appendix 14).

5.3.4.3 SF-12 Health Survey Version 2

The SF-12v2 is a well validated generic health-related quality of life questionnaire. It is a shortened form of the SF-36 Health Survey (SF-36) that assesses functional status, well-being, and health status perceptions across the following eight domains: physical functioning, role functioning-physical, bodily pain, general health, vitality, social functioning, role functioning-emotional, and mental health. The SF-12v2 has been used in the renal transplant literature and has been utilized to validate other disease-specific symptom and health status measures [Chisholm-Burns et al, 2012].

5.3.4.4 Health Economic Assessment (HEA)

Health Economic Assessments will include the following:hospitalizations recorded as number of days in the Intensive Care Unit, Step-down Unit, and general medical ward, (including emergency room visits greater than 24 hours) also non-protocol- related physician visits and emergency room visits less than 24 hours. The information will be collected by the site via a retrospective review of the subject's medical record. HEA data will include both data being routinely captured for the subject (e.g., concomitant medications) as well as data that will be used specifically for these analyses (e.g., information on hospitalizations) (Appendix 18).

5.4 Safety Assessment

Safety assessments include the following:

- Vital signs
- Adverse events graded by NCI CTCAE v. 4.03 criteria
- Local reactogenicity signs and symptoms using both the NCI-CTCAE v. 4.03 grading scale and the protocol-specified reactogenicity scale
- Systemic reactogenicity signs and symptoms using both the NCI-CTCAE v. 4.03 grading scale and the protocol-specified reactogenicity scale
- Laboratory assessments
- Urinalysis, including microscopic evaluation
- Physical examination

5.4.1 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature) will be collected at all dosing visits, and at Screening (V1), and at V12 and 13. Height will be collected at Screening only. Weight will be collected at V1, V2 and Study Completion (V13).

Vital signs will be collected as follows:

- Vital signs will be collected immediately prior to injection, at 15 and 60 minutes post Study Drug injection at study visits accompanied by injection.
- Vital signs will be collected once at Screening (Visit 1), and at Visits 12 and 13.

5.4.2 Adverse Events

See Section 5.5 Adverse Events and Other Safety Aspects for information regarding adverse event collection and data handling.

All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post Study Drug injection. AEs from the time of signing of informed consent through first dose of Study Drug should be captured on the medical history eCRF. If the AE is deemed possibly or probably related to Study Procedures prior to the first Study Drug injection, it will be recorded on the AE eCRF page. SAEs that occur from the signing of the informed consent form will be reported as per Section 5.5 and captured on the AE eCRF page. AEs and SAEs after the first dose of Study Drug should be captured on the AE eCRF page.

Data to be recorded includes the adverse event, date of onset, date of resolution, intensity, action taken with respect to Study Drug, treatment required, relationship to Study Drug and outcome of the event.

Adverse events ongoing at V13 will be followed up for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes. If the event resolves during the study, a resolution date will be documented on the case report form.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See Appendix 10 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving Study Drug is accompanied by increases in liver function testing (LFT, e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

5.4.3 Local Reactogenicity Assessments

Local reactogenicity will be evaluated one hour after each injection in the clinic. The subject must be in direct view of the clinic staff for 15 minutes following each injection, then remain in the clinic area for an additional 45 minutes for evaluation of local and systemic reactogenicity. Local reactogenicity will be evaluated via diary (once the subject is trained) for the 7 days following each injection.

Grading of reactogenicity will be done using the protocol-specified reactogenicity scale and the NCI-CTCAE v. 4.03 grading scale (Appendix 4). The daily maximum measurement of local reactogenicity signs and symptoms will be recorded.

5.4.4 Systemic Reactogenicity Assessments

Specific signs of systemic reactogenicity will be evaluated one hour after each injection (Appendix 5). The subject must be in direct view of the clinic staff for 15 minutes following each injection, then remain in the clinic area for an additional 45 minutes for evaluation of systemic reactogenicity. Vital signs, including temperature, pulse, respiration and blood pressure will be collected just prior to injection, 15 minutes post-injection and at one hour post-injection. Using the pre-injection vital signs as baseline, if a post Study Drug injection vital sign meets Grade 1-4 criteria per Appendix 5, it is to be repeated and confirmed within 5 minutes of first assessment. Systemic measurements that will be followed for 7 days are fever, fatigue and myalgia.

Grading of reactogenicity will be done using the protocol-specified reactogenicity scale (Appendix 4) and the NCI-CTCAE v. 4.03 grading scale. The daily maximum measurement of systemic reactogenicity signs and symptoms will be recorded.

5.4.5 Laboratory Assessments

Please refer to Appendix 2 for a list of laboratory tests to be performed during the study.

Blood and urine samples will be collected for the following laboratory assessments:

- Urine pregnancy testing for females of child bearing potential will be performed at the Screening Visit, prior to Study Drug when administered and according to the Schedule of Assessments, Table 1. Results must be available prior to Study Drug dosing. All pregnancy tests will be done locally.
- CMV IgG antibody will be assessed within 8 weeks prior to transplant or at Screening if no CMV IgG antibody assay has been performed within that time period by the local laboratory. CMV plasma viral load will be monitored as outlined in Table 1a. Central

laboratory measurements for routine surveillance of viremia will be performed at the following time points:

- Every other week from Day 100 to Day 200 (± 3 days).
- Monthly from Day 200 until Day 395 (±5 days).

- Local laboratory values for CMV viral load should be collected and documented in the eCRF for subjects whenever CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected within the first 12 months post first Study Drug injection and when CMV-specific AVT is initiated.
- If CMV AVT is initiated, Central lab CMV viral loads will be collected at a minimum of weekly from the time CMV specific AVT is initiated until discontinuation. Note: Central Lab turnaround time is estimated to be at least 3 days from receipt at the Central lab, not including holidays. If treatment decisions need to be made a local CMV viral load should be collected and analyzed at an Astellas approved laboratory.
- When a local lab sample is collected for CMV viral load, an additional sample must be collected and sent to the central lab. Any time a local value for CMV viral load is obtained it should be recorded in the eCRF.

As one of the plasmids of the ASP0113 vaccine codes for the pp65 antigen, the theoretical possibility of interference with the pp65 antigenemia assay has been raised. At present there are no data to suggest that such an interference occurs. However, to ensure subject safety and study integrity, sites that use pp65 antigen as their local methodology for the detection of CMV infection must adhere to the procedures defined below as a condition of participation in the trial.

- The local pp65 antigenemia results must be entered into the eCRF database within 72 hours (or next business day) of receipt to facilitate in-time monitoring of results.
- The Medical Monitor must be called within 48 hours (or next business day) if the pp65 antigenemia test is positive and the central laboratory PCR viral load result is negative.
- Both the pp65 antigenemia and the central laboratory test must be repeated within 48 hours if the local pp65 antigenemia result is positive, the central laboratory PCR viral load result is negative and the subject is treated with CMV-specific AVT. Further treatment decisions are to be discussed with the Medical Monitor.

The plasmids in the Study Drug may interfere with certain PCR assays. If a PCR assay is used that amplifies the genes UL55/gB or UL83/pp65, this could result in either a false positive viral load or unblinding of the study subject.

Sites that are determined to have an unacceptable assay in their local lab but are able to determine a Sponsor- deemed acceptable work practice flow for utilizing another acceptable local assay or methodology will be allowed to participate in the trial. Note**:** Local CMV plasma viral load testing may be performed only at a local laboratory approved by the Sponsor.

Local laboratory samples as follows per the Schedule of Assessments, Table 1:

- Hematology: red blood cells (RBC), white blood cells [(WBC) – total leukocytes], hemoglobin, hematocrit, platelets (thrombocytes), neutrophils, eosinophils, basophils, lymphocytes, monocytes.
- Biochemistry: sodium, potassium, calcium, chloride, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, CPK/CK, total protein, albumin.
- If creatinine phosphokinase (CPK) levels are 5 x the upper limit of normal (ULN), at any time during the Primary Study Period, a repeat laboratory draw should be performed. If repeat CPK is still 5x the ULN, the Medical Monitor should be notified within 2 business days for further instructions.
- Hepatic profile (total bilirubin, direct bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphase [AP]. See Appendix 10 for follow-up of liver function tests beyond the Upper Limit of Normal.
- Urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, blood, microscopic evaluation)
- Urine protein: creatinine ratio

Clinically significant laboratory results should be followed until resolution or until they are no longer clinically significant or are medically stable. Other Assessments by Central Laboratory:

- Immunogenicity: gB-specific antibody levels and T-cell responses to pp65.
- Genotypic resistance testing: Resistance to ganciclovir or valganciclovir should be assessed when there is no reduction in viral load or no change in clinical symptoms two weeks after starting valganciclovir or ganciclovir treatment for CMV viremia or disease.
- A whole blood sample for optional pharmacogenomics will be collected at Visit 2 after Randomization but prior to the first dose of Study Drug for subjects who agree to participate in the optional pharmacogenomics substudy.
- Safety labs (hematology, biochemistry, hepatic profile, urine protein:creatinine ratio and urinalysis) drawn by Home Health Care for Investigator sites utilizing this service will be analyzed by the Central Laboratory.

5.4.6 Physical Examination

Complete physical examinations (PE) will be performed at the Screening and Baseline Visits (Visit 1 and Visit 2) and at the Primary Study Period Completion/Day 395 (Visit 13). The PE will include the following: an examination of the skin, general appearance, neck (including thyroid), eyes, ears, nose, throat, lymph nodes, chest (lungs), heart, abdomen, musculoskeletal system, neurological system and any additional assessments needed to establish baseline status or evaluate symptoms or adverse events. At all other visits where a PE is performed, symptom-directed physical examinations may be done. If Screening is done > 3 days prior to Randomization, the PE must be repeated on the day of Randomization.

The Investigator or qualified medical personnel who routinely perform these evaluations in this patient population will conduct the examination, determine findings, and assess any abnormalities as to clinical significance.

5.4.7 Home Health Care Service

An optional Home Health Care Service is available through the Sponsor in lieu of the subject coming in to the Investigative site for the following visits

- Post-Dosing Visits 3, 7 and 11 for clinical laboratory collection.
- CMV Plasma Viral Load Testing Visits (Central Laboratory Testing) at Day 100, 114, 128, 142, 156, 170, 198, 230, 290, 320, 350, and 380. (Days 100 and 198 CMV testing must correspond appropriately with visit windows for Visits 3 and 11 in order to be combined).

Home Health Care visits are not allowed at any visit where a physical assessment, adverse event assessment or Immunology blood collection is due. For sites that choose to use the service, the home health care nurse will report vital signs and subject complaints at this visit via Sponsor approved source documents. The nurse will collect blood samples, process and ship them appropriately to the Central or local laboratory. Local CMV viral load testing may only be performed at a local laboratory approved by the Sponsor.

This service may not be available in all regions.

5.4.8 Long Term Follow-Up

Subjects will be contacted by telephone at 6 months after Day 395, then annually for the next 4 years for long-term safety related to the DNA vaccine. Items to be assessed by questionnaire and available patient records include mortality, development of any new cancer, development of infection requiring hospitalization or resulting in death, graft survival, creatinine and erythema and/or induration at the sites of immunizations (see Appendix 17). Creatinine values will be recorded if they have been collected within 3 months prior to the follow-up telephone contact and are in the subject's available medical records.

During the long-term follow-up period, if an SAE is identified and deemed possibly or probably related to the study medication, an SAE report on the SAE worksheet must be sent to the sponsor per Section 5.5.6.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a Study Drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.
- The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.

5.5.2 Adverse Events of Special Interest

The following definitions should be used to properly record and report adverse events for the study.

5.5.2.1 Adverse Events Commonly Associated with Vaccines

The following adverse events have been reported with other vaccines and will be subject to specific monitoring:

- Acute local vaccines reactions including as local pain, redness, swelling or induration
- Acute systemic vaccine reactions including as anaphylaxis and convulsions
- Late vaccine reactions including demyelinating disorders (e.g., Guillain-Barré syndrome, neuritis, neuropathy).

5.5.2.2 Infection

- Bacterial, fungal and viral infections and the following information will be collected: Treatment with a antimicrobial agent for a specific clinical syndrome (not prophylaxis)
- Positive cultures, pathologic identification of microbial agents or significant serological changes related to clinical symptoms
- Typical clinical presentation documented by investigator or appropriate consultant.

In addition, the following information should be collected for potential BK viral infections:

- Renal biopsy results, if performed.

Definitions of opportunistic, EBV and BK infections are provided in Appendices 8 and 9, respectively.

5.5.2.3 Post-Transplant Lymphoproliferative Disorder (PTLD)

Diagnosis of PTLD should be made following review of tissue specimens. The anatomic staging of PTLD will be captured, specifically if the allograft or Central Nervous System (CNS) is involved. PTLD will be classified according to the criteria in Appendix 12. Additionally, if available, ancillary pathologic information related to cell phenotype, clonality, presence of EBV in the tissue specimen, and donor vs. recipient origin will be collected.

Tissue samples should be interpreted by a hematopathologist or pathologist who is familiar with the histopathologic features of PTLD. If as a matter of the subject's routine medical evaluation tissues are examined for the presence of EBV by *in situ* hybridization, the cell of origin (B, T, null, mixed) is determined or radiographic evaluation is performed to document the extent of disease (e.g., CT scans) this information will be captured on the CRF.

5.5.3 Definition of Serious Adverse Events (SAEs)

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

- Results in death.
- Is life threatening (an adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death).
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in congenital anomaly, or birth defect.
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).
- Other medically important events.
- The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., Study Drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

All of the events of interest noted above should be recorded on the (e)CRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' and the SAE worksheet.

The Sponsor has a list of events that they classify as “always serious” events. If an adverse event is reported that is considered to be an event per this classification as “always serious”, additional information on the event may be requested.

5.5.4 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the Study Drugs could not be ruled out".

Causal relationship to the Study Drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on or drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.5 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated.
5-Death	Death related to AE.

5.5.6 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact the Sponsor by fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor by fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

The Investigator should fax the SAE Worksheet to:

[redacted]
Fax number [redacted]
International Fax: [redacted]
Email: [redacted]

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and on the (e)CRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the Study Drug.

Spontaneously reported possibly or probably related SAEs that occur outside of the study-defined SAE reporting period**,** i.e., the Long Term Follow-up, should also be sent to the sponsor in accordance with the protocol defined SAE reporting guidelines.

The Sponsor or Sponsor's designee will submit expedited safety reports (e.g. IND Safety Reports) to the regulatory agencies (e.g. FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (e.g. EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor/delegated CRO will notify all investigators responsible for ongoing clinical studies with the Study Drug of all SAEs which require submission per local IRB/IEC requirements.

The investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

For Suspected Unexpected Serious Adverse Reactions (SUSAR) from a blinded trial, unblinded CIOMS-I report will be submitted to the authorities and IRB/IEC where required.

5.5.7 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the adverse event progresses to an ″SAE″, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to Appendix 10 Liver Safety Monitoring and Assessment for detailed instructions on Drug Induced Liver Injury (DILI).

5.5.8 Monitoring of Common Serious Adverse Events

Common serious adverse events are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in Appendix 11 Common Serious Adverse Events for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common serious adverse events” as specified in Appendix 11 Common Serious Adverse Events. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.5.6 Reporting of Serious Adverse Events.

5.5.9 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within one year post first Study Drug injection, the investigator should report the information to the Sponsor as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure

for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the Study Drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the Study Drug is judged as ″possible″ by the investigator.
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.
- If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the Sponsor as an SAE.

5.5.10 Emergency Procedures and Management of Overdose

In the event of suspected ASP0113 overdose, the subject should receive supportive care and monitoring. The Medical Monitor/Expert should be contacted.

5.5.11 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

Not Applicable

5.7 Other Measurements, Assessments or Methods

5.7.1 Blood Sample for Future PGx Analysis (Retrospective PGx Analysis)

A PGx research study may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. After randomization, but prior to the first dose of Study Drug (see schedule of assessments), subjects who consent to participate in the retrospective pharmacogenomics assessment will have a 5 mL sample of whole blood collected for possible retrospective PGx analysis. This sample will be collected using a vacutainer tube containing EDTA. After collection, gently invert the blood sample 8 to 10 times. The blood collection tube may either be stored upright at 4°C for up to 5 days prior to shipment

or stored frozen at -20°C or below at the site for extended storage. Samples will be shipped to a Sponsor designated banking CRO.

Labels should uniquely identify each sample and contain at least:

- Protocol number (0113-CL-2001),
- Subject number, and
- Purpose and biological matrix (i.e., “biobanking”, “whole blood”).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See Appendix 16, Retrospective PGx Sub-study for further details on the banking procedures.

5.8 Total Amount of Blood

The total amount of blood to be collected for central and local laboratory assessments per subject should not exceed 61 mL at any study visit and is expected to be approximately 504 mL total for the study. Central laboratory volume drawn is estimated not to exceed 50 mL per visit. As local laboratory amounts vary between institutions, the total amount may vary.

This total blood volume does not include the volume for the CMV viremia assessments when assessments are not done per schedule, nor does it include pharmacogenomics or genotypic resistance testing, as this will be performed only as required.

Refer to the Laboratory Manual for more details regarding blood collection.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

6.1.1 Study and Treatment Discontinuation

Study and Treatment Discontinuation:

Subjects will be withdrawn from investigational study treatment and all follow- up assessments and will only be followed for mortality through public records if the following occurs:

- Withdrawal of consent by the subject.

Treatment Only Discontinuation:

Subjects will be withdrawn from investigational study treatment if any of the following occur, however, they should continue to be followed according to the protocol Schedule of Assessments (Table 1) and Long Term Follow-up Schedule of Assessments, except post-dose Day 14 safety and laboratory and reactogenicity assessments/visits for those doses not given.

- Investigator's decision that further treatment is not in the best interest of the subject.
- Graft failure.
- Pregnancy (female subjects only).
- Local reactogenicity with a grade ≥ 3 based on the criteria defined in Appendix 4 and is confirmed by a health care professional and reported as a Drug Related Adverse Event.
- Systemic reactogenicity, for any grade ≥ 3 fever or any grade 4 systemic reaction within one week of vaccination and is confirmed by a health care professional and reported as a Drug Related Adverse Event (Appendix 5).
- Anaphylaxis Grade ≥ 3 per NCI ver. 4.03 criteria.

Subjects who discontinue investigational treatment for these or for other reason(s) but do not withdraw consent should remain in the study and continue to be followed according to the visit schedule through the Long-term Follow-up Period. All study procedures should be completed for these subjects, with the exception of the post-dose Day 14 safety laboratory and reactogenicity assessments/visits for those doses that are not given. Subjects not willing to participate in the study procedures should be asked if they would be willing to be followed annually for mortality through the Long-term Follow-up Period.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If

the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

A Statistical Analysis Plan (SAP) will be written by the responsible biostatistician of APGD to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to database lock, a final review of data and tables, listings and forms (TLFs) meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications will also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

Unless specifically stated otherwise, all efficacy comparisons will be tested at 1-sided 0.05 level and safety comparisons will be tested at 2-sided 0.05 level. Confidence intervals for efficacy estimates, if provided, will be constructed at 90% level.

7.1 Sample Size

In a recent study of prophylactic valganciclovir given at 900 mg/day for 100 days to donor CMV-seropositive/recipient CMV seronegative (D+R-) kidney transplant recipients [Humar, 2006], CMV viremia, defined as CMV viral load > 600 copies/mL, was seen through one year in 83 of 163 subjects [50.9%, 95% CI = (43.0%, 58.8%)]. In another study [Couzi, 2012], CMV infection, defined as two consecutive positive Polymerase Chain Reaction (PCR) assay results, was seen in 11 of 32 subjects (34.4%, 95% Confidence Interval (CI) = (18.6%, 63.2%)), respectively. Pooled from these two studies by weighted average, it is estimated that placebo rate is 46% (70% weight on Humar's result). A sample size of 64 subjects per arm will allow the study to have 80% power to detect a reduction in CMV viremia to 25% due to ASP0113 at 52 weeks using a 1-sided test with a type 1 error rate of 5%. To allow for loss to follow-up, 70 subjects per arm will be enrolled for a total sample size of 140 subjects.

7.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in classification specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The Full Analysis Set will consist of all subjects who are randomized and receive at least one dose of Study Drug and have at least one post dose viral load assessment by central laboratory. This will be the primary analysis set for efficacy analyses and for summaries of demographic and baseline characteristics.

7.2.2 Per Protocol Set (PPS)

The Per Protocol Set (PPS) will be specified in detail prior to locking and unblinding the final study database. The PPS will include all subjects in the FAS who had no major protocol violations or other conduct during the study that would make a subject non-evaluable. Complete criteria will be defined in the SAP. The PPS will be used for secondary analyses of efficacy variables and for selected demographic and baseline characteristics.

7.2.3 Safety Analysis Set (SAF)

The Safety Analysis Set consists of all randomized subjects who received at least one dose of randomized Study Drug and for whom any data is reported after first dose of Study Drug.

The SAF will be used for summaries of demographic, baseline characteristics, and all safety related variables.

7.2.4 Pharmacogenomics Set (PGS)

The pharmacogenomics set consists of all randomized subjects who consent to participate in the optional pharmacogenomics sub-study and who have a blood sample collected during the Baseline Visit, after Randomization but prior to the first dose of Study Drug. The PGS will be used for all pharmacogenomic analyses.

7.3 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by treatment group using the SAF, FAS and PPS.

Continuous variables will be summarized by descriptive statistics (e.g., n, mean, standard deviation, minimum, median, and maximum) and discrete variables will be summarized by the number and percentage of subjects in each category.

7.4 Analysis of Efficacy

Primary efficacy analysis will be conducted on the FAS. The PPS will be used to assess the robustness of the selected efficacy analysis based on the FAS.

7.4.1 Analysis of Primary Efficacy Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint, the incidence of CMV viremia (defined as plasma viral load ≥ 1000 IU/mL by central assay) through one year post first Study Drug injection, in subjects receiving a kidney from a living or deceased donor, will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by use of anti-thymocyte globulin (ATG) and by receipt of a kidney from a living or deceased donor.

The null and alternative hypotheses for this comparison are:

H0: Common Odds Ratio = 1.

H1: Common Odds Ratio < 1.

The 1-sided p-values will be calculated, together with the 90% 2-sided confidence interval for the odds ratio. The primary analysis will be conducted using the FAS. Determination of the primary endpoint in subjects in the FAS with missing central laboratory CMV viral load values is described in Section 7.9.

7.4.1.2 Secondary Analysis

The same analysis of the primary efficacy endpoint as described in 7.4.1.1 will be conducted using the PPS.

7.4.1.3 Subgroup Analysis

The Breslow-Day test will be used to assess the consistency of the odds ratio across the strata. In the event that the Breslow-Day test is significant at the 0.10 level, tabulations of the treatment effect will be provided for each strata to assess the strength of possible treatment-by-strata interactions.

7.4.2 Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study include:

- Incidence of adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease through one year post first Study Drug injection.
- Incidence of CMV viremia (defined as plasma viral load ≥ the lower limit of quantification [LLOQ]) by central assay through one year post first Study Drug injection.
- Incidence of adjudicated CMV-specific antiviral therapy.
- Incidence of graft survival through one year post Study Drug injection.
- Incidence of subject survival through one year post Study Drug injection.

The secondary efficacy endpoints will be each analyzed using the same CMH method described in 7.4.1.1.

All analyses of secondary endpoints will be performed using FAS and PPS.

7.4.3 Analysis of Exploratory Endpoints

The exploratory endpoints in this study include:

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ 1000 IU/mL by central assay) through one year post first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of CMV viral load of ≥ 1000 IU/mL by central assay through one year post first Study Drug injection.
- Peak CMV viral load through one year first Study Drug injection.
- Viral load area under the curve (AUC), as a measure of "cumulative viral load" through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Incidence of viral resistance to ganciclovir or valganciclovir through one year post Study Drug injection as determined by a central laboratory assay.
- Incidence of biopsy-proven (T or B cell) rejection (BPAR)(Banff 2007 Grade ≥ 1) through one year post Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at the last study visit calculated using the 4 variable MDRD formula.
- Incidence of clinically treated acute graft rejection rate through one year post Study Drug injection.
- Health economic and outcomes research (HEOR) scores.
- Patient-reported outcomes:
    - EQ-5D (EuroQol-5 dimensions 5 levels) will be used as a preference-based utility measure of patients' quality of life.
    - KTQ (Kidney Transplant Questionnaire) will be used to evaluate transplant-specific patients' quality of life.
    - SF-12v2 (Short Form Health Survey version 2) will be used to evaluate the overall patients' quality of life.
- Healthcare resource utilization:
    - Resource use will be collected including the following: hospitalizations recorded as number of days in the Intensive Care Unit, Step-down Unit, and general medical ward, (including emergency room visits greater than 24 hours);) also non-protocol- related physician visits and emergency room visits less than 24 hours.

Number of episodes of CMV viral load of ≥ 1000 IU/mL and number of episodes of adjudicated CMV-associated disease will each be compared between treatments using Poisson regression controlling for follow-up period and stratification factors.

The incidence endpoints will be each analyzed using CMH method described in 7.4.1.1.

The survival endpoints (time to first event) will be each analyzed in a Cox proportional hazards model. The Cox model will include the randomization factors. The common hazard ratio and confidence limits will be estimated. The 1-sided p-values for testing the hypothesis that the hazard ratio is equal to unity will be calculated. The Kaplan-Meier estimates of survival curves for the treatment groups will be displayed.

Peak CMV viral load and AUC through one year post first Study Drug injection will be compared using Wilcoxon rank-sum tests.

The change from baseline to last visit in estimated glomerular filtration rate (eGFR) and the changes in Health Economic and Outcomes Research (HEOR) scores and patient reported quality of life scores will be each compared between treatment groups using an ANCOVA model with the change in score as the outcome and the treatment as the factor and baseline value as the covariate.

All analyses of exploratory endpoints will be performed using the FAS.

7.4.4 Immunogenicity Analysis

T-Cell responses to pp65 and gB-specific antibody levels will be compared at each time point using the Wilcoxon rank-sum test. Graphic presentation of the mean of T-Cell responses to pp65 and gB-specific antibody levels over time by treatment group will also be provided.

Immunogenicity analysis will be performed using the FAS.

7.5 Analysis of Pharmacogenomic Data

Pharmacogenomic data will be displayed using descriptive statistics for each treatment group on PGS.

7.6 Analysis of Safety

7.6.1 Adverse Events

Treatment emergent (TE) is defined as the study period of time from the first dose of Study Drug through one year post first Study Drug injection. A TE adverse event (AE) is defined as any AE that started or worsened during the TE period. Unless otherwise stated, all analyses described in this section will be performed on events and measures during this period.

For the purpose of safety assessments in this study, adverse events recorded during the period between the informed consent and the first dose of Study Drug will be classified as Medical History.

The coding dictionary for this study will be the Medical Dictionary for Regulatory Activities (MedDRA). It will be used to summarize adverse events (AEs) by system organ class and/or preferred term. The version of MedDRA to be used will be determined prior to final database lock.

The following summaries of adverse events will be provided by system organ class and preferred term for TE adverse events:

- Number and percentage of subjects with AEs
- Number and percentage of subjects with drug-related AEs
- Number and percentage of subjects with serious AEs
- Number and percentage of subjects with AEs leading to permanent discontinuation of Study Drug injection
- Number and percentage of subjects with serious drug related AEs
- Number and percentage of subjects with drug related AEs leading to permanent discontinuation of Study Drug injection
- Number and percentage of subjects with AEs by severity (worst degree)
- Number and percentage of subjects with drug related AEs by severity (worst degree)
- Number and percentage of subjects with AEs by relationship to Study Drug

Drug-related AE is defined as any AE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

All summaries of serious TEAEs described above will also be performed for serious AEs that were reported any time after the start of Study Drug administration.

The number of deaths and of subjects with AEs of special interest that occur during the TE period will also be summarized.

Subgroups analyses for age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), and the use of anti-thymocyte globulin (ATG) (yes/no) will be performed for the following summaries:

- TEAEs
- Drug-related TEAEs
- Serious TEAEs
- TEAEs leading to permanent discontinuation of Study Drug
- Serious AEs during the study
- AEs of special interest during the study

All AEs will be listed.

7.6.2 Clinical Laboratory Evaluation

Analyses of clinical laboratory data will be performed on laboratory evaluations during the study.

Clinical laboratory tests (e.g., hematology, biochemistry) will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group at each

scheduled visit. Additionally, the change from baseline will be summarized by treatment group and visit.

The shift in select laboratory tests from baseline (or final visit for renal function tests) to select time points (worst value during study, Months 1, 2, 3, 6, 9, and 12) will be summarized.

Potentially clinically significant (PCS) laboratory test results that are observed any time during the TE period will be tabulated and compared across all treatment groups using a chi-square test. This analysis will be conducted only on subjects that did not meet the PCS criteria at baseline.

Subgroups analyses for age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), and the use of anti-thymocyte globulin (ATG) (yes/no) will be performed for the following summaries:

- Summary of clinical laboratory tests at each scheduled visit
- Summary of change from baseline at each scheduled visit
- Summary of PCS laboratory values

7.6.3 Vital Signs Evaluation

Vital signs (oral temperature, systolic and diastolic blood pressure, weight, respiration rate and pulse rate) will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group at each scheduled visit. Additionally, the change from baseline in these parameters will be summarized by treatment group and visit.

The number and percent of subjects that had a systolic blood pressure ≥ 160 mmHg at any time will be tabulated by treatment group for subjects whose baseline value was < 160 mmHg. Subjects that did not have a baseline measurement will be excluded from the analyses. The number and percent of subjects that had a diastolic blood pressure ≥ 100 mmHg at any time and whose baseline value was less than 100 mmHg will be summarized similarly.

The analysis of vital signs described above will also be performed by the following subgroups: age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), deceased donor and the use of anti-thymocyte globulin (ATG) (yes/no).

7.6.4 Physical Examination

Physical results will be listed by treatment group.

7.7 Protocol Deviations and Other Analyses

Protocol deviations as defined in Section 8.1.6 Protocol Deviations will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

Two interim safety and efficacy analyses are planned. The first one will occur when 50 subjects (approximately 25 in each group) have completed the month 6 visit assessment. The second interim analysis will occur when 90 subjects (approximately 45 per group) have completed the 6 month visit assessment.

A Data Monitoring Committee (DMC), external from the Sponsor, will be established to review safety and efficacy data at each interim look. A detailed description of the DMC, its role in this clinical trial, and the timing of the scheduled reviews will be provided in the DMC Charter.

7.8.1 Safety

Data from all subjects who have been enrolled will be included in the safety reviews. All data submitted to the DMC will remain blinded to Astellas personnel involved in the study. A detailed safety data interim analysis plan will be included in the DMC Charter.

7.8.2 Efficacy

Interim efficacy analyses will be performed for the sole purpose of assessing futility. Interim efficacy analyses will include all available data from subjects who have completed the 6 month visit. At each interim, Bayesian predictive probability (*BPP*) that the observed rate of viremia in the ASP0113 treatment group being at least 25% less than the observed viremia rate in the placebo treatment group will be calculated. If the $BPP \leq 0.20$, it will be concluded that ASP0113 meets futility criterion.

Extensive simulations were conducted to assess the operating characteristics of this futility criterion, and the results are satisfactory. The simulation algorithm, scenarios and results will be summarized in the SAP for this protocol.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

The primary efficacy endpoint of CMV viremia is based on central laboratory assessments of CMV viral load which are taken every 2 weeks from Day 100 to Day 198, monthly from

Day 230 to Day 395 and all for cause (suspect CMV syndrome or CMV tissue-invasive disease) viral loads. In the primary efficacy analysis, subjects who are lost to follow-up will be imputed as having viremia. Otherwise, viremia will not be imputed in cases where central lab CMV viral load data are missing. Only observed viral loads meeting the definition of viremia will be counted.

However, secondary analyses of the primary endpoint will explore the consequences of alternative imputations. These will be described in the Statistical Analysis Plan.

The start and stop dates of AEs and concomitant medication will be imputed where necessary prior to unblinding. The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

Subjects who do not receive the Study Drug to which they have been randomized will be analyzed as treated for safety analysis and as randomized for efficacy analysis.

See the SAP for details of the definitions for windows to be used for analyses by visit.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at both local and central laboratories. Central laboratory data will be transferred electronically to the Sponsor or designee at predefined intervals during the study. The laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

For Screen failures the informed consent, demographic data, reason for failing, inclusion and exclusion criteria and Adverse Events will be collected in the eCRF.

Subject Assessment of Reactogenicity: A diary will be used for the 7-day reactogenicity follow-up. The subject will enter the data directly into the diary that will be provided at each Study Drug injection visit.

8.1.1.1 Patient Reported Outcomes (pPRO)

Subject diaries and questionnaires will be completed by the subject on paper. The investigator or site designee should review the diaries and questionnaire data while the subject is at the site. The investigator or site designee will enter the subject diary and questionnaire data directly into the EDC system.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of Study Drug details
- Reason for premature discontinuation (if applicable)
- Randomization number

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2 "Specification of Source Documents") when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of

the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science of the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. (e)CRF completion will be described in the (e)CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit at the end of the Primary Study Period (Day 395). The Long Term Follow Up will continue after the end of trials' Primary Study Period.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of Study Drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding one year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies, or for APEB/APEL-sponsored studies within one year after last subject out (LSO) or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.

The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the Study Drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the vaccine and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The Sponsor will notify the site/investigator if the NDA/MAA is approved or if the IND/IMPD is discontinued. The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the CRFs supplied for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval

or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the regulatory authority, and the IRB/IEC.

Amendments to this protocol must be signed by the Sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Insurance of Subjects and Others

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Data Monitoring Committee (DMC)

A DMC external from the Sponsor will be chartered to oversee the safety of subjects and review of the futility analysis. The DMC will consist of independent reviewers who are not directly involved in the conduct of the study.

10.2 Other Study Organization

10.2.1 Adjudication Committee (AC)

An Adjudication Committee (AC) external from the Sponsor will be chartered to adjudicate all subjects for cases of CMV syndrome, CMV tissue-invasive disease and CMV-specific antiviral therapy. The AC will consist of a multidisciplinary group of independent clinician-scientists who are not directly involved in the conduct of the study.

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Company Reports:

ASP0113 Investigator's Brochure, Astellas Pharma Global Development, Inc..

12 APPENDICES

12.1 Appendix 1: List of Excluded Concomitant Medications

- Investigational research products through completion of Day 395 visit (Visit 13)
- Planned Alemtuzumab and, anti-CD20 antibodies (including rituximab), eculizumab or bortezomib are not allowed from Day of Randomization through the Primary Study Period (Day 395). These treatments may be given after the Day of Randomization if clinically indicated.
- Prophylactic use of CMV immunoglobulin.
- Live attenuated vaccines within one month (30 days) prior to each dose of Study Drug.
- Subunit or killed vaccines within 14 days before any Study Drug injection.
- Anticoagulants, within 5 half-lives of Study Drug administration, including but not limited to vitamin K antagonists, heparin or its derivatives, low molecular weight heparin, factor X inhibitors, or thrombin inhibitors. Low dose anticoagulants that are used for prevention of deep vein thrombosis and antiplatelet agents are allowed.

12.2 Appendix 2: Laboratory Tests

Central Laboratory Testing		
Laboratory Test	**Visit**	**Parameters to be Analyzed**
Central CMV Plasma Viral Load	Every other week from Day 100-200, then monthly through end of study Day 395, for cause (suspect CMV syndrome or CMV tissue-invasive disease), at least once a week from initiation of CMV-specific AVT until it is completed, any time a local CMV viral load is obtained	• CMV plasma viral load by central lab assay
Genotypic resistance testing	When viremia is present with no reduction in viral load or clinical improvement after 2 weeks of treatment with valganciclovir and ganciclovir	• Resistance to valganciclovir and ganciclovir
Immunogenicity	V2, V5, V6, V9, V10 & V13	• gB-specific antibody levels • Immunological assays measuring T-cell responses to pp65
Pharmacogenomics (PGx) – optional –whole blood sample	V2	• Genomic analyses
Local Laboratory Testing		
Laboratory Test	**Visit**	**Parameters to be Analyzed**
CMV Screening	Up to 8 weeks prior to transplant through day of transplant or at Screening (V1)	• CMV serostatus
Hematology	Screening (V1) and Visits 2-11 & 13	• Red blood cells • White blood cells (total leukocytes) • Hemoglobin • Hematocrit • Platelets (thrombocytes) • Neutrophils (ANC) • Eosinophils • Basophils • Lymphocytes • Monocytes
Biochemistry	Screening (V1) and Visits 2-11 & 13	• Sodium • Potassium • Calcium • Chloride • Phosphorus • Glucose • BUN

		• Creatinine • Creatine phosphokinase (CPK)/Creatine kinase (CK) • Total protein • Albumin
Hepatic Profile	Screening (V1) and Visits 2-11 & 13	• Total bilirubin • Direct bilirubin • Alkaline Phosphatase • AST • ALT
Urinalysis	Screening (V1) and Visits 2-11 & 13	• pH • specific gravity, • protein, glucose, • ketones, • bilirubin • blood • microscopic evaluation
Urine protein: creatinine ratio	Screening (V1) and Visits 2-11 & 13	• Protein: creatinine ratio
Urine Pregnancy Test (females of childbearing potential only)	Screening (V1), V2, V4, V6, V8, V10, 12 & 13	• Human Chorionic Gonadotropin (hCG)

12.3 Appendix 3: 4 Variable MDRD

Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula

For creatinine in mg/dL:

$eGFR = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}]$

[American Journal of Kidney Diseases 2002; 39(Suppl 1): S76-S110.Vol 39, Issue 2, Supplement 1, Pages S76-S110, Feb 2002]

12.4 Appendix 4: Grading of Local Reactogenicity

Local Reaction To Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life - Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.0 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration / Swelling **	2.0 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

12.5 Appendix 5: Grading of Signs of Systemic Reactogenicity

Systemic (General)*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life –Threatening Grade 4)**
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Vital Signs†**				
Fever (°C)*** (°F)***	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	> 40 > 104
Tachycardia-beats per minute	Increase in heart rate 5-15 beats/minute	Increase in heart rate 16-30 beats/minute	Increase in heart rate > 30 beats/minute	ER visit or hospitalization for arrhythmia
Bradycardia-beats per minute	Decrease in heart rate 5-10 beats/minute	Decrease in heart rate 11-15 beats/minute	Decrease in heart rate > 15 beats/minute	ER visit or hospitalization for arrhythmia
Hypertension (systolic)-mm Hg	Increase in systolic blood pressure (SBP) 20-30 mmHg	Increase in SBP 31 mmHG - 40 mmHg	Increase in SBP > 40 mmHg	ER visit or hospitalization for malignant hypertension
Hypotension (systolic)-mm Hg	Decrease in SBP 5 mmHg	Decrease in SBP 5.1 mmHg to 10.0 mmHg	Decrease in SBP to > 10.0 mmHg	ER visit or hospitalization for hypotensive shock
Respiratory Rate-breaths per minute (at rest)	17-20	21-25	> 25	Intubation

* Grading of Systemic Reactogenicity.

**Subject should be at rest for all vital sign measurements.

***Oral temperature; no recent hot or cold beverages or smoking.

†**Pre- dosing vital signs are to be used as baseline values for determining changes post Study Drug Injection.**

Reference: Modified for the Renal Transplant Population from the Guidance for Industry titled "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" issued by FDA on September 2007.

12.6 Appendix 6: Grading of Acute Kidney Allograft Rejection

2007 Update to the Banff 97 Diagnostic Categories for Renal Allograft Biopsies

Category	Global Assessment	Histopathological Findings
1	**Normal**	
2	**Antibody-mediated changes** (may coincide with categories 3, 4 and 5 and 6)	Due to documentation of circulating antidonor antibody, and C4d or allograft pathology C4d depletion without morphologic evidence of active rejection C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e., g0, cg0, ptc0, no ptc lamination). Cases with simultaneous borderline changes or ATN are considered indeterminate
	Acute antibody-mediated rejection[1]	C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):
	Grade I	ATN-like minimal inflammation
	Grade II	Capillary and/or glomerular inflammation (pct/g > 0) and/or thromboses
	Grade III	Arterial – v3
	Chronic active antibody-mediated rejection[1]	C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries
3	**Borderline** (may coincide with categories 2 and 5 and 6)	"Suspicious" for acute T-cell-mediated rejection This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2, or t3) with minor interstitial infiltrate (i0 or i1) or interstitial infiltrate (i2, i3) with mild (t1) tubulitis
4	**T-cell mediated rejection** (TCMR, may coincide with categories 2 and 5 and 6)	
	Acute T-cell-mediated rejection (Type/Grade)	
	Grade IA	Cases with significant interstitial infiltration (> 25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
	Grade IB	Cases with significant interstitial infiltration (> 25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
	Grade IIA	Cases with mild-to-moderate intimal arteritis (v1)
	Grade IIB	Cases with severe intimal arteritis comprising > 25% of the luminal area (v2)
	Grade III	Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
	Chronic active T-cell-mediated rejection	"Chronic allograft arteriopathy" (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)
5	**Interstitial fibrosis and tubular atrophy**	No evidence of specific etiology (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointersitial features)
	Grade I	Mild interstitial fibrosis and tubular atrophy (< 25% cortical area)
	Grade II	Moderate interstitial fibrosis and tubular atrophy (26-50% of cortical area)
	Grade III	Severe interstitial fibrosis and tubular atrophy/loss (> 50% of cortical area)
6	**Other**	Changes not considered to be due to rejection-acute and/or chronic (for diagnosis see full article Table 14; may include isolated g, cg or cv lesions and coincide with categories 2, 3, 4 and 5)

[1] Suspicious for antibody-mediated rejection if C4d (in the presence of antibody) or alloantibody (C4d+) not demonstrated in the presence of morphologic evidence of tissue injury.

Reference: Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel F, et al. Banff '07 classification of renal allograft pathology: updates and future directions. Am J Transplant. 2008;8:753-60.

12.7 Appendix 7: Definition of CMV Disease in Solid Organ Transplant Recipients

Disease type	Probable	Definite
CMV syndrome	One or more of the following: 1. Fever > 38°C for at least 2 days 2. New or increased malaise 3. Leukopenia 4. ≥ 5% atypical lymphocytes 5. Thrombocytopenia 6. Elevation of hepatic transaminases (ALT or AST) to 2 x upper limit of normal (applicable to nonliver transplant recipients) plus evidence of CMV in blood by viral culture, antigenemia or a DNA/RNA-based assay	Clinical and laboratory findings as in 'probable' case and no other cause of symptoms/signs identified
Pneumonia[1]	Signs and/or symptoms of pulmonary disease in the absence of other documented cause plus evidence of CMV in blood and/or[3] bronchoalveolar lavage (BAL) fluid by viral culture, antigenemia or a DNA/RNA-based assay	Signs and/or symptoms of pulmonary disease plus detection of CMV in lung tissue by culture, immunohistochemical analysis or *in situ* hybridization[4] with or without evidence of CMV in blood or BAL fluid by viral culture, antigenemia (BAL) or a DNA/RNA-based assay
Gastrointestinal disease	Symptoms of upper or lower gastrointestinal disease plus macroscopic mucosal lesions on endoscopy plus evidence of CMV in blood or biopsy tissue by viral culture, antigenemia or an RNA/DNA-based assay	Symptoms or signs of upper or lower gastrointestinal disease plus detection of CMV in gastrointestinal tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]
Hepatitis	Elevation of bilirubin and/or hepatic enzymes in the absence of other documented cause of hepatitis[2] plus evidence of CMV in blood by antigenemia or a DNA/RNA-based assay	Elevation of bilirubin and/or hepatic enzymes plus detection of CMV in liver tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]

Appendix 7: Definition of CMV Disease in Solid Organ Transplant Recipients (continued)

Disease type	Probable	Definite
CNS disease	CNS symptoms in the absence of other documented cause plus evidence for CMV in CSF samples by viral culture, or DNA/RNA-based assay	CNS symptoms plus detection of CMV in CNS tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]
Retinitis	Not applicable	Lesions typical of CMV retinitis must be confirmed by an ophthalmologist or by detection of CMV by culture or PCR of vitreous fluid
Other tissue invasive disease (nephritis, cystitis, myocarditis, pancreatitis, etc.)	Evidence of organ dysfunction in the absence of other documented cause[2] plus evidence of CMV in blood by viral culture, antigenemia or DNA/RNA-based assay	Symptoms/signs of organ dysfunction plus detection of CMV in affected tissue by culture, immunohistochemical analysis or *in situ* hybridization[4]

[1]Superinfection or co infection with other pathogens may occur and should be noted when present.

[2]If affected organ is the allograft, acute rejection must be excluded as a cause for the clinical symptoms.

[3]The detection of CMV in both BAL and peripheral blood strengthens the evidence for probable CMV pneumonitis.

[4]Although, immunohistochemistry and *in situ* hybridization techniques are more sensitive for the detection of CMV-infected cells than morphologic examination, the presence of typical cytomegalovirus inclusions should be considered evidence of definite disease.

Reference:

Humar A and Michaels M. American society of Transplantation Recommendations for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation. *Am J Transplantation.* 2006;6:262-274.

12.8 Appendix 8: Opportunistic Infections

- Viral infections
  - HHV-1: Herpes simplex 1 (HSV 1)
    - Herpes labialis
  - HHV-2: Herpes simplex 2 (HSV 2)
    - Herpes genitalis
  - HHV-3: Varicella zoster virus (VZV)
    - Chicken Pox
    - Shingles
  - HHV-4: Epstein Barr virus
    - Mononucleosis
    - Burkitt's lymphoma
    - Nasopharyngeal carcinoma
    - Post-transplant lymphoproliferative disorder (PTLD)
    - Oral hairy leukoplakia
  - HHV-6: Human herpes virus 6
    - Roseola subitum
  - HHV-7: Human herpes virus 7
    - Roseola subitum
    - Pityriasis rosea
  - HHV-8: Human herpes virus 8
    - Kaposi's sarcoma
    - Effusion lymphoma
    - Multifocal Castleman's disease
  - Simian virus 40
  - Jacob-Creutzfeld
  - BK virus

Appendix 8: Opportunistic Infections *continued*

- Bacterial infections
  - Legionellosis pneumophilia
  - Nocardiosis
  - Listeriosis monocytogenes
- Fungal infections
  - Aspergillus
  - Candida
  - Coccidioides
  - Cryptococcus
  - Histoplasma
  - Mucormycosis

Diagnosis of infection must be supported by appropriate laboratory tests, histopathology, serologies, radiologic findings or culture.

Dubberke ER and Brennan DC. *Core Concepts in Renal Transplantation.* Chapter 9 Infectious Complications in Renal Transplant Recipients (A. Chandraker et al. (eds)

12.9 Appendix 9: Special Infections Related to Kidney Transplant

Epstein Barr Virus (EBV) Infection:

Active, asymptomatic EBV infection is defined by the presence of a detectable EBV viral load as measured by a nucleic acid amplification assay. Asymptomatic infection may also be identified in lymphoid rich histopathologic specimens.

EBV Disease:

EBV disease is defined by the presence of active EBV infection with symptoms or signs attributable to the virus.

BK Virus Infection:

BK virus infection (replicative infection) defined as quantitative BK viral DNA load, in blood or urine above the detection threshold for the given laboratory's assay. BK infection is classified as either BK viruria or BK viremia or both. While the presence of decoy cells in urine on cytology is suggestive of BK infection, confirmation with a specific test (e.g., PCR) is required.

BK Virus Associate Nephropathy (BKVAN):

Proven BK virus associated nephropathy is defined by evidence of BK virus infection and the presence of:

- Renal biopsy associated with:
    - an acute tubular necrosis-like picture *or*
    - interstitial nephritis mimicking acute rejection *or*
    - chronic allograft nephropathy with confirmation of the presence of BK virus by electron microscopy, immunohistochemistry or *in-situ* hybridization for BK virus. Although intra-nuclear viral inclusions are usually seen, their presence is not mandatory for a diagnosis of BKVAN.

For purposes of this study, subjects with *presumptive* BKVAN diagnosed in the presence of renal allograft dysfunction and a positive BKV DNA PCR result from blood in a subject with no viral inclusions at light microscopy and negative immunohistochemistry/*in-situ* hybridization should be classified as BK virus infection (i.e. BK viremia rather than BKVAN).

12.10 Appendix 10: Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy who reveals an increase of serum aminotransferases (AT) to > 3 × baseline value and greater than 3X ULN , or bilirubin > 2 × baseline value and greater than 2X ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies in which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. As local laboratories are utilized for this study, the investigator must report a repeat confirmation of moderate or severe liver abnormalities to the Medical Monitor within 48-72 hours of the test results. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3× baseline value & > 3x ULN	or	> 2× baseline value & > 3xULN
Severe*	> 3× baseline value & > 3x ULN	and	> 2× baseline value & > 3x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

ALT or AST > 8× ULN
ALT or AST > 5× ULN for more than 2 weeks
ALT or AST > 3× ULN and INR > 1.5 (If INR testing is applicable/evaluated).
ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that will be activated for any study subject with severe abnormalities as determined by the medical monitor. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the Study Drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a Serious Adverse Event (SAE). The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to Study Drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
Obtain a history of exposure to environmental chemical agents.
Based on the subject's history, other testing may be appropriate including:

- acute viral hepatitis (A,B, C, D, E or other infectious agents)
- ultrasound or other imaging to assess biliary tract disease
- other laboratory tests including INR, direct bilirubin

Consider gastroenterology or hepatology consultations.
Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

ALT or AST > 8 × ULN
ALT or AST > 5 × ULN for more than 2 weeks
ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5) (If INR testing is applicable/evaluated)

ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant). The two "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006 Apr;15(4):241-3.]

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.11 Appendix 11: Common Serious Adverse Events

The following is a list of serious adverse events that the Sponsor considers to be associated with the disease state being studied. **The list does NOT change your reporting obligations or prevent the need to report an adverse event meeting the definition of an SAE as detailed in Section 5.5.3 Definition of Serious Adverse Event (SAE)**. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". You are required to follow the requirements detailed in Section 5.5.6 Reporting of Serious Adverse Events (SAE).

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicates that they occur more frequently with Study Drug, an expedited IND safety report may be submitted to the FDA.

- Kidney transplant rejection
- Kidney allograft loss
- Blood creatinine increased
- Diabetes mellitus
- Hyperglycemia
- Increase blood glucose

12.12 Appendix 12: Categories of Post Transplant Lymphoproliferative Disorder (PTLD)

Categories of PTLD are the following:

- Early Lesions
  - Reactive plasmacytic hyperplasia
  - Infectious mononucleosis-like
- Polymorphic PTLD
- Monomorphic PTLD (classify according to lymphoma classifications)
  - B cell neoplasms
    - Diffuse large B cell lymphoma (immunoblastic, centroblastic, anaplastic)
    - Burkitt/Burkitt-like lymphoma
    - Plasma cell myeloma
    - Plasmacytoma-like lesions
    - Maltoma
  - T cell neoplasm
    - Peripheral T cell lymphoma, unspecified type
    - Anaplastic large cell lymphoma (T or null cell)
    - Hepatosplenic gamma-delta T cell lymphoma
    - Other (i.e., T-NK type)
- Hodgkin lymphoma and Hodgkin lymphoma-like PTLD

Reference:

AJT Infectious Disease Community. Epstein-Barr virus and lymphoproliferative disorders after transplantation. *Am J Transplantation* 2004; 4(Suppl. 10): 59-65.

12.13 Appendix 13: EQ-5D Questionnaire

Note that the below is an example; subjects will be provided with forms to be completed.

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

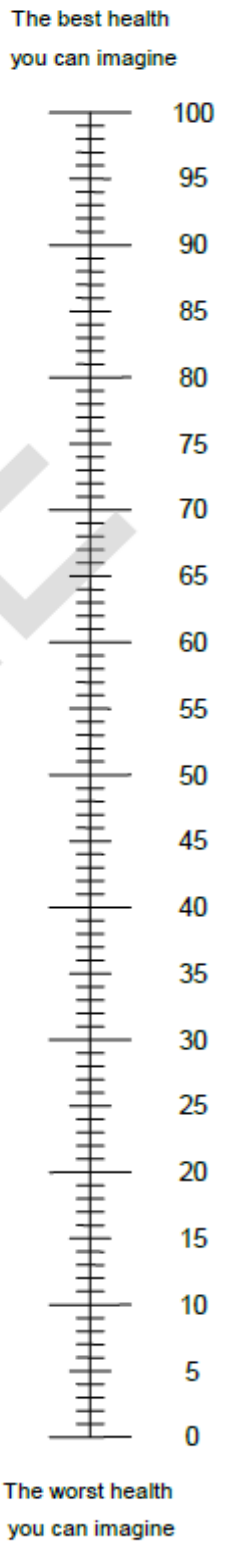
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix 13: EQ-5D Questionnaire continued

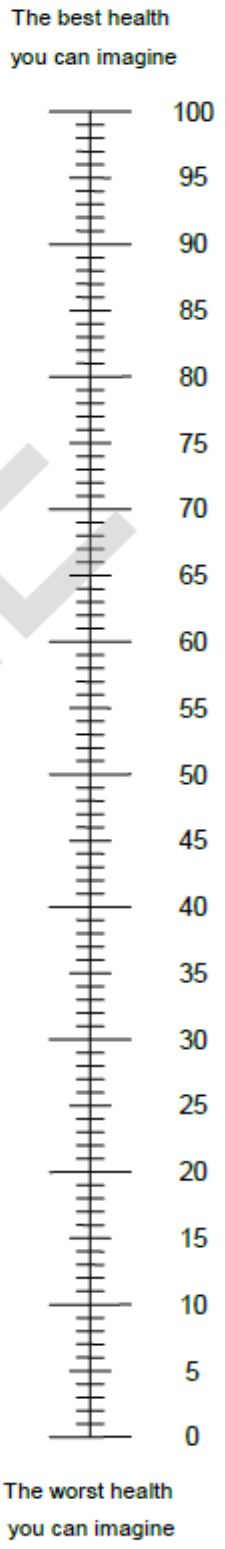
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



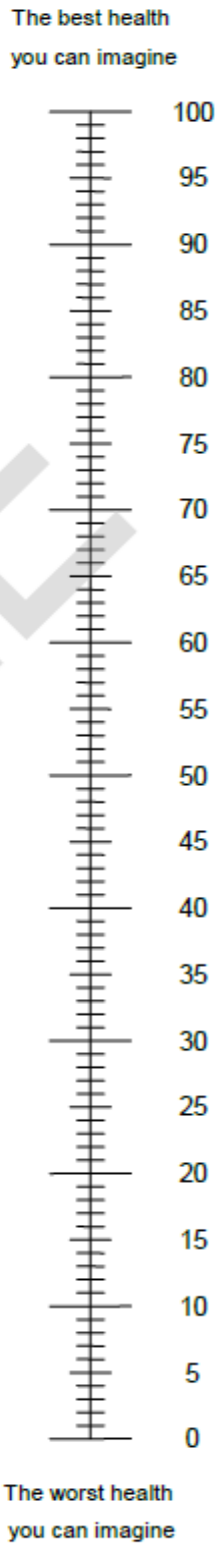
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



12.14 Appendix 14: Kidney Transplant Questionnaire (KTQ-34)

INSTRUCTION: This questionnaire asks for your views about your health-related quality of life. Please read each question very carefully and mark the response that best reflects your experience. Please note that the different sections ask for different types of responses. Please choose only one answer for each item and do not skip any items.

	Amount of Time In the Past Two Weeks						
	All of the time	Most of the time	A Good Bit of the time	Some of the time	A little of the time	Hardly Any of the time	None of the time
1. How often in the past two weeks have you felt weak?	1	2	3	4	5	6	7
2. How often in the past two weeks have you felt impatient?	1	2	3	4	5	6	7
3. How often in the past two weeks have you felt depressed?	1	2	3	4	5	6	7
4. How often in the past two weeks have you felt stubborn?	1	2	3	4	5	6	7
5. How often in the past two weeks have you felt sluggish?	1	2	3	4	5	6	7
6. How often in the past two weeks have you felt anxious?	1	2	3	4	5	6	7
7. How often in the past two weeks have you felt fear or panic related to graft rejection?	1	2	3	4	5	6	7
8. How often in the past two weeks have you felt uncertain about your future?	1	2	3	4	5	6	7
9. How often in the past two weeks have you felt worried?	1	2	3	4	5	6	7
10. How often in the past two weeks have you felt protective of your transplant?	1	2	3	4	5	6	7
11. How often in the past two weeks have you felt irritable, difficult to get along with?	1	2	3	4	5	6	7
12. How often in the past two weeks have you felt generally frustrated?	1	2	3	4	5	6	7
13. How often in the past two weeks have you felt low in energy?	1	2	3	4	5	6	7
14. How often in the past two weeks have you felt dizzy or lightheaded?	1	2	3	4	5	6	7

Appendix 14: Kidney Transplant Questionnaire (KTQ-34) continued:

	Amount of Trouble or Distress						
	A Very Great Deal	A Great Deal	A Good Deal	A moderate Amount	Some	Very Little	None
15. In the past two weeks, how much trouble or distress have you had because of excessive appetite?	1	2	3	4	5	6	7
16. In the past two weeks, how much trouble or distress have you had because of excessive hair growth?	1	2	3	4	5	6	7
17. In the past two weeks, how much trouble or distress have you had because of very little strength?	1	2	3	4	5	6	7
18. In the past two weeks, how much trouble or distress have you had because of increased tiredness?	1	2	3	4	5	6	7
19. In the past two weeks, how much trouble or distress have you had because of excessive weight?	1	2	3	4	5	6	7
20. In the past two weeks, how much trouble or distress have you had because of acne?	1	2	3	4	5	6	7
21. In the past two weeks, how much trouble or distress have you had because of difficulty sleeping?	1	2	3	4	5	6	7
22. In the past two weeks, how much trouble or distress have you had because of trembling in your body, hands or fingers?	1	2	3	4	5	6	7
23. In the past two weeks, how much trouble or distress have you had because of ache or pain in your joints?	1	2	3	4	5	6	7
24. In the past two weeks, how much trouble or distress have you had because of ache or pain in your feet and legs?	1	2	3	4	5	6	7
25. In the past two weeks, how much trouble or distress have you had because of ache or pain in your shoulder and arms?	1	2	3	4	5	6	7
26. In the past two weeks, how much trouble or distress have you had because of muscle cramps?	1	2	3	4	5	6	7

Appendix 14: Kidney Transplant Questionnaire (KTQ-34) continued:

	Amount of Trouble or Distress						
	A Very Great Deal	A Great Deal	A Good Deal	A moderate Amount	Some	Very Little	None
27. In the past two weeks, how much trouble or distress have you had because of not seeing clearly?	1	2	3	4	5	6	7
28. In the past two weeks, how much trouble or distress have you had because of swollen or bleeding gums?	1	2	3	4	5	6	7
29. In the past two weeks, how much trouble or distress have you had because of swelling in your ankles or legs?	1	2	3	4	5	6	7
30. In the past two weeks, how much trouble or distress have you had because of abdominal bloating?	1	2	3	4	5	6	7
31. In the past two weeks, how much trouble or distress have you had because of shortness of breath?	1	2	3	4	5	6	7
32. In the past two weeks, how much trouble or distress have you had because of headaches?	1	2	3	4	5	6	7
33. In the past two weeks, how much trouble or distress have you had because of your medication dosing schedule or the number of pills you take?	1	2	3	4	5	6	7
34. In the past two weeks, how much trouble or distress have you had because of decreased sexual interest or sexual activities?	1	2	3	4	5	6	7

12.15 Appendix 15: SF-12

SF-12v2™ Health Survey

(SF-12 v2 Standard, US Version 2.0)

To be completed by the PATIENT

Identification Number

Event

Directions: *This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. If you need to change an answer, completely erase the incorrect mark and fill in the correct circle. If you are unsure about how to answer a question, please give the best answer you can.*

Today's Date (MM/DD/YY)

__ __ / __ __ / __ __

Shade circles like this: ● **Not like this:** ⊗ ✓

Mark only one answer for each question. Please do not mark outside the circles or make stray marks on the questionnaire.

	Excellent	Very Good	Good	Fair	Poor
01. In general, would you say your health is:	○	○	○	○	○
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
02. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○		
03. Climbing several flights of stairs	○	○	○		
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
04. Accomplished less than you would like	○	○	○	○	○
05. Were limited in the kind of work or other activities	○	○	○	○	○
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
06. Accomplished less than you would like	○	○	○	○	○
07. Did work or activities less carefully than usual	○	○	○	○	○
08. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely
	○	○	○	○	○
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...	All of the time	Most of the time	Some of the time	A little of the time	None of the time
09. Have you felt calm and peaceful	○	○	○	○	○
10. Did you have a lot of energy	○	○	○	○	○
11. Have you felt downhearted and depressed	○	○	○	○	○
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	○	○	○	○	○

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-1 of 1-

12.16 Appendix 16: Retrospective Pharmacogenomics (PGx) Sub-Study

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to ASP0113 in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide one 5 ml tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas. Detailed collection, storage, and shipment procedures will be included in the Laboratory Manual for the study.

BANKING CRO STORAGE AND SAMPLE CODING

Once received at the banking CRO, the samples will be assigned a unique sample code (second code) and stored frozen. A table linking the subject number (first code) with the newly-assigned sample code (second code) will be kept by the banking CRO. PGx analysis will be conducted using the second code only.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety. Prior to initiating any analysis on the banked samples, the Astellas ethical committee (AREC) must approve the analysis plan.

DISPOSAL OF PGx SAMPLES / DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Retrospective PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.17 Appendix 17: Long-term Follow-up Questionnaire

Subjects will be contacted by telephone annually for 4 years starting at 1.5 years after the first injection of Study Drug to evaluate for long-term safety related to the DNA vaccine. Items to be assessed by questionnaire and available medical records include mortality, development of any new cancer, development of infection requiring hospitalization, graft survival, creatinine and local immune-mediated reactions.

During the long-term follow-up period, if an SAE is identified and deemed possibly or probably related to the study medication, an SAE report on the SAE worksheet must be sent to the sponsor per Section 5.5.6.

The following information will be collected at each of the contact time points:

1. Subject mortality, including primary cause of death and date of death (if applicable).
2. Development of any new/recurrent cancer (name).
3. Development of infection requiring hospitalization or resulting in death (name of infecting agent, or medications or laboratory data leading to diagnosis).
    - The subject will be asked whether he/she has been diagnosed with any new medical conditions requiring hospitalization to solicit this information.
4. Creatinine values will be recorded if they have been collected within 3 months prior to the follow-up telephone contact and are in the subject's available medical records.
5. Initiation of dialysis.
6. Subsequent kidney transplant.
7. Immune-mediated reactions.
    - The subject will be asked if he/she has had any redness or swelling at the site of the injection.

12.18 Appendix 18: Health Economic Assessment (Inpatient and Outpatient Utilization)

Are there any Inpatient Care visits to report? □Yes □No

If Yes, please record the number of days the patient was admitted to:

Admission Unit/Floor

ICU Days_____
# of Days

Step-down Unit Days_____
# of Days

Hospital General Medical/Surgical Ward Days_____
# of Days

Was there an Emergency Room visit greater than 24 hours (without admittance)? □Yes □No

If yes, please indicate the number of Emergency Room days_____
# of days

Primary Reason (Diagnosis) for Admission:_____

If a US site, please insert the ICD-9 code for the diagnosis.

If more than one Inpatient Care visit to report, please record diagnosis/ICD-9 code for each admission, and the number of days as noted above.

Are there any Non- Protocol- related Physician visits to report? □ Yes □No

If Yes, please indicate the number of of visits:

Physician Visits_____
# of visits

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 2

I. The purpose of this amendment is:

Substantial Changes
1. Definition of Terms, Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Revise to reflect that the Screening Period may begin -14 days from transplant up to day of Randomization.
RATIONALE:
Subjects are discharged frequently within several days after transplant and since the first dose of vaccine is one month after transplant, increasing the screening period to start up to 14 days prior to transplant allows a site to screen a subject at their pre-transplant evaluation. Some sites may adjust medications used for induction therapy and CMV prophylaxis based on whether or not the subject has agreed to participate in the trial. Some sites prefer to discuss study objectives, procedures and obtain Informed Consent prior to the transplant procedure when the subject is in a stable condition.
2. Change the definition of CMV viremia to plasma viral load ≥1000 IU/mL
DESCRIPTION OF CHANGE:
Revise CMV viremia definition from plasma viral load ≥250 IU/mL to plasma viral load ≥1000 IU/mL.
RATIONALE:
There is no known threshold of CMV viremia which correlates with CMV disease because assays have not been standardized across institutions at this time. However, in the Phase 2 trial, in hematopoetic stem cell recipients, the plasma viral load threshold that was associated with a reduction in clinical outcomes was ≥1000 IU/mL.
3. Change the use of anti-thymocyte globulin (ATG) as induction therapy for stratification criteria.
DESCRIPTION OF CHANGE:
Remove the wording “as induction therapy” and added “Prior to Randomization” when describing the use of anti-thymocyte globulin.
RATIONALE:
The stratification criteria for ATG was expanded from use for induction therapy to day of Randomization because ATG is commonly used to treat delayed graft function and acute rejection immediately post transplantation. In order to assess the population of patients who will receive the vaccine post approval, ATG is being allowed up to day of Randomization.

4. Change in anti-viral prophylaxis (AVP) dose adjustment wording
DESCRIPTION OF CHANGE:
Revise the period of adjustment for the CMV anti-viral prophylaxis (AVP) to after the Day of Randomization.
RATIONALE:
Clarifies the time point when the CMV AVP can be adjusted.
5. Additional wording to define AVP
DESCRIPTION OF CHANGE:
Add wording to clarify that Investigators may use their clinical judgment for interrupting/ adjusting dosage of AVP.
RATIONALE:
Provide clarity on guidance for interrupting/adjusting AVP dosage.
6. Additional wording regarding CMV resistance.
DESCRIPTION OF CHANGE:
Insert additional wording if resistance to CMV AVT is suspected.
RATIONALE:
To allow for investigator discretion in regards to suspected resistance to CMV AVT.
7. Add vital signs and evaluation of subjects 15 minutes post-study drug injection.
DESCRIPTION OF CHANGE:
A 15 minute post study drug administration vital signs is added.
RATIONALE:
To further monitor the safety of a subject post study drug administration.
8. Revise Inclusion Criteria
DESCRIPTION OF CHANGE:
Add “per regulatory label (package insert)” to Inclusion Criteria 5.
RATIONALE:
To allow subjects to be dosed based on their renal function, as noted in the package insert for their region.
9. Add Exclusion Criteria
DESCRIPTION OF CHANGE:

Add Exclusion Criteria 5 to exclude subjects that may require dialysis on the day of Randomization.
RATIONALE:
Subjects cannot be receiving dialysis on the day of Randomization because it is a contraindication to the use of valganciclovir which is required therapy for the first 80 days of the trial.
10. Delete Exclusion Criteria
DESCRIPTION OF CHANGE:
Delete Exclusion Criteria 8 which excluded subjects that had an episode of hyper acute or acute rejection prior to Randomization.
RATIONALE:
Hyperacute or acute rejection is not expected to affect the efficacy of the vaccine. It is the drugs used to treat the episodes of rejection which may interfere with the efficacy of the vaccine because of their suppressive effects on the immune system. Therefore, instead of excluding a subject with hyperacute and acute rejection, medications which significantly suppress the immune response are added to exclusion criteria.
11. Revise Exclusion Criteria
DESCRIPTION OF CHANGE:
Add eculizumab, bortezomib, intravenous immunoglobulin (IVIG) and plasmapheresis as prohibited from Day of Transplantation through the Day of Randomization to Exclusion Criteria 9.
RATIONALE:
Eculizumab, bortezomib, IVIG and plasmapheresis, because they significantly suppress immune responses, and therefore, may interfere with effectiveness of the vaccine.
12. Revise Exclusion Criteria
DESCRIPTION OF CHANGE:
Add further clarification to Exclusion Criteria 11 regarding contraindications for prophylaxis of CMV viremia/disease with valganciclovir or ganciclovir.
RATIONALE:
To ensure the criteria reflects any reason a subject would not be able to receive valganciclovir/ ganciclovir at Randomization.
13. Revise Exclusion Criteria
DESCRIPTION OF CHANGE:
Add clarification to the time frame to contraindications for intramuscular injections referenced in Exclusion Criteria 12.

RATIONALE:
To eliminate subjects that are likely to have a contraindication to IM injections at Baseline and throughout the Primary Study Period.
14. Revise Exclusion Criteria
DESCRIPTION OF CHANGE:
Add further clarification to Exclusion Criteria 13 regarding timeframe for AST or ALT criteria.
RATIONALE:
Subjects may require time for AST/ALT to return to normal post operatively.
15. Concomitant Medication Restriction or Requirements, CMV Prophylaxis
DESCRIPTION OF CHANGE:
Clarify the number of doses the subject can miss prior to Randomization and dose adjustment criteria per the Investigators clinical judgment.
RATIONALE:
To provide parameters for clinically indicated dosage holds or subject missed doses that will still qualify the subject for the study.
16. Concomitant Medication Restriction or Requirements, *Pneumocystis jiroveci Pneumonia Prophylaxis*
DESCRIPTION OF CHANGE:
Add wording for dose adjustments and interruptions to *Pneumocystis jiroveci Pneumonia Prophylaxis*.
RATIONALE:
To provide further clarification to support dose adjustment for clinical indications.
17. Concomitant Medication Restriction or Requirements, Prohibited Concomitant Medications (Drugs and Therapies)
DESCRIPTION OF CHANGE:
Revise wording for Alemtuzumab and Rituximab as well as adding additional prohibited medications. Also clarify time periods for prohibited medications.
RATIONALE:
Alemtuzumab (T cell depleting agent), ATG (T cell depleting agent) and anti-CD 20 antibodies (B cell depleting agent) may interfere with effectiveness of the vaccine. Therefore, if a subject is planned to receive any one of these agents through the primary study period they are excluded. However, it is not ethical to prevent subjects from receiving these agents if they are clinically indicated, and, to prevent protocol violations and drop-outs,

subjects may receive these agents if clinically indicated after they have been Randomized into the trial.
18. Concomitant Medication (Drugs and Therapies)
DESCRIPTION OF CHANGE:
Clarify that the medications used for anesthesia during the transplant will not be recorded.
RATIONALE:
To clarify procedures other than the transplant using anesthesia must have those anesthetic agents recorded. Medications used for anesthesia are difficult to record and are not expected to affect the outcome of the trial.
19. Concomitant Medication Restriction or Requirements, Prohibited Concomitant Medications (Drugs and Therapies)
DESCRIPTION OF CHANGE:
Insert wording to note that IVIG and plasmapheresis are not allowed from Day of Transplant through the Day of Randomization.
RATIONALE:
IVIG and plasmapheresis significantly suppress immune responses and, therefore, are likely to interfere with the efficacy of the vaccine.
20. Discontinuation Criteria
DESCRIPTION OF CHANGE:
Clarify wording to reflect that grading should be confirmed by a health care professional's (HCP).
RATIONALE:
To specify that grading > 3 as assessed by the subject, must be confirmed by a HCP.
21. Discontinuation Criteria
DESCRIPTION OF CHANGE:
Add anaphylaxis as discontinuation criteria.
RATIONALE:
Anaphylaxis of Grade $\geq$ 3 per NCI Criteria warrants discontinuation from the study.
22. Endpoints for Evaluation; Exploratory Endpoints
DESCRIPTION OF CHANGE:
Simplify the language of Healthcare utilization to be recorded.
RATIONALE:

Previous language and data to be collected were duplicate data and clarification given on how to record inpatient and outpatient days.
23. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Additional Home Health Care visits are added with criteria expanded to provide clarification to visit windows and allowed procedures.
RATIONALE:
To provide more flexibility for sites using the service for subjects that live remotely.
24. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Moved the screening window from 'Day 10 to Day 30' to 'Day -14 to Day of Randomization (Day 30)'.
RATIONALE:
Screening window is moved to accommodate Screening prior to Transplant.
25. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Change to standardize collection of concomitant medications for all subjects to 14 days prior to Transplant.
RATIONALE:
As screening can now take place from 14 days prior to Transplant until 30 days post Transplant, all subjects will have concomitant medications collected during that time period.
26. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Add urine protein: creatinine ratio
RATIONALE:
Urine protein: creatinine ratio is an important indicator of renal disease post transplant
27. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Add the criteria for recording of AEs as medical history until first dose of study drug and SAEs from signing of the Informed Consent being reported per SAE criteria.
RATIONALE:

As Screening will now occur prior to transplant, criteria related to the reporting and capturing of AEs and SAEs prior to the administration of the Study Drug are defined.
28. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Add HCV PCR RNA donor and recipient criteria to be recorded if available.
RATIONALE:
This additional information is important when available to further assess safety issues that might occur during the trial and possible relatedness to the underlying disease and not administration of the vaccine.
DESCRIPTION OF CHANGE:
Add wording for stable subjects that have Home Health Care visits for blood draws will only draw Central Lab CMV samples.
RATIONALE:
To eliminate the possibility of the use of an unapproved local laboratory being used and a potential false positive result.
29. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Add wording to note that subject should not have a temperature of ≥100.4 prior to a study drug injection.
RATIONALE:
To accurately assess subject safety post vaccination.
30. Flow Chart and Schedule of Assessments
DESCRIPTION OF CHANGE:
Add criteria for the repeat of vital signs post injection.
RATIONALE:
If vital signs meet Grade 1-4 criteria per Appendix 5, they will be confirmed for appropriate subject treatment, if needed.
31. Revise Exploratory Efficacy Assessment
DESCRIPTION OF CHANGE:
Clarify time point for eGFR exploratory assessment.
RATIONALE:

Clarified the time point is the last study visit for those subjects that do not go through the entire trial to Day 395/Month 13.
32. Add Laboratory Assessments
DESCRIPTION OF CHANGE:
Add phosphorus to local laboratory samples collected.
RATIONALE:
Correction to missing information.
33. Revise Long Term Follow-up language
DESCRIPTION OF CHANGE:
Spontaneously reported SAEs during the Long Term Follow-up that are possibly or probably related to the study drug are to be reported using the SAE worksheet.
RATIONALE:
SAEs that are possibly or probably related to study drug and have been reported by the subject or are found on hospital record reviews are required to be reported on SAE worksheets, as the subjects are still enrolled in the trial.
34. Revise Dose/Dose Regimen and Administration Period
DESCRIPTION OF CHANGE:
Add that an injection should not be given if a subject has a temperature ≥100.4.
RATIONALE:
To accurately assess subject safety post vaccination.
35. Clarify Definitions of Adverse Events and Serious Adverse Events
DESCRIPTION OF CHANGE:
Clarified that the transplant surgery that occurs on Day 0 is not considered an AE or SAE.
RATIONALE:
This is a planned event not considered an AE or SAE.
36. Appendix 5: Grading of Signs of Systemic Reactogenicity
DESCRIPTION OF CHANGE:
Define predose vital signs to be collected
RATIONALE:
To define what vital signs are to be used as baseline.

37. Appendix 10: Liver Safety Monitoring Assessment
DESCRIPTION OF CHANGE:
Change the AST/ALT and TV from the ULN to the subject's baseline value and ULN.
RATIONALE:
Subjects are permitted to begin the study with higher than normal ALT/AST and TB levels. This takes into account their possible higher baseline values.
38. Appendix 10: Liver Safety Monitoring Assessment
DESCRIPTION OF CHANGE:
Criteria are added for when Investigator is to contact Medical Monitor based on local laboratory values.
RATIONALE:
Additional criteria are needed as local labs are being used for this study.
39. Appendix 16: Retrospective Pharmacogenomics (PGx) Sub-Study
DESCRIPTION OF CHANGE:
Delete text referencing genetic testing and rename "exploratory" to "Retrospective".
RATIONALE:
Clarification needed for possible PGx analysis.

Non-Substantial Changes
1. Update List of Abbreviations
DESCRIPTION OF CHANGE:
Revise abbreviations for Deceased Donor Criteria and Herpes Simplex Virus. Also add abbreviation for Intravenous Immunoglobulin.
RATIONALE:
To correct list of abbreviations to match body of protocol.
2. Clarify Key Study Terms
DESCRIPTION OF CHANGE:
Clarify definitions for Adverse Events and Randomization.
RATIONALE:
Add wording to further define an adverse event occurring due to study procedures and revise definition for Randomization to reflect change in screening period.

3. Update Planned Study Period
DESCRIPTION OF CHANGE:
Revise First Subject in to Q42013
RATIONALE:
To update study timelines.
4. Update Planned Total Number of Study Centers and Locations
DESCRIPTION OF CHANGE:
Remove Brazil and United Kingdom
RATIONALE:
Additional countries are not necessary for enrollment.
5. Minor wording clarifications
DESCRIPTION OF CHANGE:
Minor wording changes in Study Design, Discontinuation Criteria and Section 2.2.1
RATIONALE:
To provide further clarity to Investigators.
6. Exclusion Criteria 13
DESCRIPTION OF CHANGE:
Add wording to define when this contraindication is valid.
RATIONALE:
To provide further clarity to Investigators.
7. Transplant Information
DESCRIPTION OF CHANGE:
Add HCV PCR RNA to footnote.
RATIONALE:
This additional information is necessary when available to assess safety issues that might occur during the trial, but are related to the patient having active hepatitis C and not administration of the vaccine.
8. Healthcare resource utilization
DESCRIPTION OF CHANGE:

The data to be collected is changed to hospital days, physician visits and emergency room visits without admission.
RATIONALE:
To clarify necessary data or collection and provide clarification to sites on data entry.
9. Laboratory Assessments
DESCRIPTION OF CHANGE:
Wording is added so that a local CMV laboratory sample will be drawn with a Central Lab sample.
RATIONALE:
To add clarification to when local CMV's are drawn.
10. Laboratory Assessments
DESCRIPTION OF CHANGE:
Add wording to note that HHC safety labs will be analyzed by the Central Lab.
RATIONALE:
To allow for regional limitations for local lab samples to be drawn by the HHC and clarify that the Central lab will be the standard collection in all regions.
11. Statistical Methodology
DESCRIPTION OF CHANGE:
Remove mention of soft lock for the database lock.
RATIONALE:
The term is not universally understood so it is removed.
12. Analysis of Safety, Adverse Events, Clinical Laboratory Evaluation & Vital Signs Evaluation
DESCRIPTION OF CHANGE:
Remove "deceased donor criteria" and revise the ATG for induction use for defining AEs, Clinical Laboratory Evaluations and Vital Signs used for the Analysis of Safety.
RATIONALE:
Deceased donor criteria are not being collected and ATG for induction is removed as criteria and changed to ATG (at any time).

13. Appendix 7
DESCRIPTION OF CHANGE:
Add wording for definite retinitis.
RATIONALE:
To further clarify methods of detection.
14. Dosing and Administration of Study Drug(s) and other Medication(s)
DESCRIPTION OF CHANGE:
Add text indicating that information regarding syringes is located in the Pharmacy Manual.
RATIONALE:
To provide clarification to sites for where they can locate instructions regarding study drug administration.
15. Administrative Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes, e.g., typos, format, consistency throughout the protocol.
RATIONALE:
To provide clarifications to the protocol, and to ensure complete understanding of study procedures.

II Amendment Summary of Changes:

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS **List of Abbreviations**	
Page 11	
WAS:	
DCD	Deceased Donor Criteria
IS AMENDED TO:	
~~DCD~~ DD**C**	Deceased Donor Criteria
Page 12	
WAS:	
HHV	Herpes Simplex Virus
IS AMENDED TO:	
HHV	**Human** Herpes ~~Simplex~~ Virus
Page 13	
ADDED:	
IVIG	**Intravenous Immunoglobulin**

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS **Definition of Terms**
Page 15; Adverse Event
WAS:
An adverse event is any untoward medical occurrence in a subject administered a Study Drug which does not necessarily have a causal relationship with the treatment.
IS AMENDED TO:
An adverse event is any untoward medical occurrence in a subject **who was** administered a Study Drug ~~which~~ **or has undergone study procedures that** does not necessarily have a causal relationship with the treatment.
Page 16; Randomization
WAS:
The action to allocate a subject to a treatment group. In this study, randomization occurs after the subject has met all inclusion and exclusion criteria between days 10-30 +/- 3 days after the transplant date.
IS AMENDED TO:
The action to allocate a subject to a treatment group. In this study, randomization occurs after the subject has met all inclusion and exclusion criteria between days **-14/+**~~10 –~~**30 relative to** ~~+/- 3~~ ~~days after~~ the transplant date.

IV. Synopsis
Page 17; Planned Study Period
WAS:
First subject in (FSI) 3Q2013; Last Subject Out (LSO) 2Q2017 Long-term Follow-up Period LSO 4Q2021
IS AMENDED TO:
First subject in (FSI) **4Q2013**~~3Q2013~~; Last Subject Out (LSO) 2Q2017**, (Primary Study Period)** Long-term Follow-up Period LSO 4Q2021

IV. Synopsis **2.1 Study Objectives**
Page 17; Study Objectives, # 1 *Page 37; 1st bullet point*
WAS:
To evaluate the efficacy of ASP0113 compared to placebo in reducing the incidence of CMV viremia (defined as plasma viral load ≥ 250 IU/mL by central laboratory assay) through one year post first Study Drug injection in CMV-seronegative subjects receiving a kidney from a CMV-seropositive donor.
IS AMENDED TO:
To evaluate the efficacy of ASP0113 compared to placebo in reducing the incidence of CMV viremia (defined as plasma viral load ≥ ~~250~~**1000** IU/mL by central laboratory assay) through one year post first Study Drug injection in CMV-seronegative subjects receiving a kidney from a CMV-seropositive donor.

IV. Synopsis
Page 17; Planned Total Number of Study Centers and Location(s)
WAS:
Locations: Countries may include, but are not limited to: United States, Canada, Germany, Spain, United Kingdom, France, Australia and Brazil
IS AMENDED TO:
Locations: Countries may include, but are not limited to: United States, Canada, Germany, Spain, ~~United Kingdom,~~ France~~,~~ **and** Australia ~~and Brazil~~

IV. Synopsis
Pages 17-18; Study Design Overview
WAS:
This is a randomized, double-blind, placebo-controlled trial. 140 CMV-seronegative subjects who have received a kidney from a living or deceased CMV-seropositive donor will be randomized 30 days ± 3 days after transplantation (Day 0)

in a 1:1 ratio to ASP0113 or placebo.

Randomization will be stratified by use of anti-thymocyte globulin as induction therapy and by receipt of a kidney from a living or deceased donor.

Subjects will receive either 5 doses of ASP0113 or 5 doses of placebo on Days 30 ± 3, 60 ± 5, 90 ± 5, 120 ± 5, and 180 ± 5 in relation to the day of transplant.

Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) continuously until the day of Randomization to prevent CMV disease. Subjects will then receive CMV-specific anti-viral prophylaxis (AVP) until 100 days post transplant.

Subjects can have CMV-specific AVP interrupted or dose adjusted per standard of care after initiation if renal function is compromised or there are toxicities related to the administration of the AVP. In all subjects plasma will be collected for central laboratory CMV viral load testing every two weeks from Day 100 through Day 200, then monthly through last study visit.

In cases where CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected from the first Study Drug injection through Day 395, an additional central and local laboratory CMV viral load will be collected at the time of the first CMV symptom recognition.

CMV-specific anti-viral therapy (AVT) should be initiated for CMV disease and can be initiated for CMV viremia based on the central or local laboratory results and standard of care.

If CMV-specific AVT is initiated, both a central and a local CMV viral load will be obtained at a minimum of weekly from the time CMV-specific AVT is initiated until discontinuation.

In addition, each time a local CMV viral load sample is collected, a plasma sample will also be collected and sent to the central laboratory for CMV viral load testing.

Subjects will be followed for one year post first Study Drug injection (Study completion/Day 395) for CMV viremia, CMV syndrome, CMV tissue-invasive disease, and CMV-specific AVT, graft survival, creatinine and subject survival through the Study Completion/Day 395 Visit.

Subjects will be followed for one year post first Study Drug injection for resistance to valganciclovir or ganciclovir. Viral resistance will be measured if the viral load has not decreased 2 weeks after initiating CMV-specific AVT or when there is no improvement in clinical signs and symptoms two weeks after initiating valganciclovir or ganciclovir for CMV viremia and/or disease.

Immunogenicity to pp65 and gB will be assessed prior to Dose 1, two weeks after Dose 2, prior to Dose 3, two weeks after Dose 4, prior to Dose 5 and at the last study visit.

Subjects will be evaluated for local and systemic reactogenicity one hour after each Study Drug injection and for 7 days by subject reporting via diary after each Study Drug injection. All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post first Study Drug injection.

Subjects will be contacted by telephone annually at 6 months after Day 395, then annually for the next 4 years, to evaluate long-term safety related to the deoxyribonucleic acid (DNA) vaccine. Mortality, development of any new malignancies, development of infection

requiring hospitalization or resulting in death, graft survival, creatinine and erythema and/or induration at the injection sites will be assessed by questionnaire and available patient records.

IS AMENDED TO:

This is a randomized, double-blind, placebo-controlled trial.

140 CMV-seronegative subjects who have received a kidney from a living or deceased CMV-seropositive donor will be randomized 30 days ± 3 days after transplantation (Day 0) in a 1:1 ratio to ASP0113 or placebo.

Prior to Randomization**, subjects** will be stratified by use of anti-thymocyte globulin ~~as induction therapy~~ and by receipt of a kidney from a living or deceased donor.

Subjects will receive either 5 doses of ASP0113 or 5 doses of placebo on Days 30 ± 3 60 ± 5, 90 ± 5, 120 ± 5, and 180 ± 5 in relation to the day of transplant.

Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) **through** ~~continuously until~~ the day of Randomization to prevent CMV disease. **(The subject can miss up to two doses of valganciclovir or ganciclovir during this time period for any reason).**
Subjects will then **continue to** receive CMV-specific anti-viral prophylaxis (AVP) **with valganciclovir or ganciclovir** until 100 days post transplant.

Subjects can have **valganciclovir or ganciclovir** ~~CMV-specific AVP~~ interrupted**,** ~~or~~ dose adjusted **or replaced by other CMV-specific AVP** per standard of care after **the day of Randomization** ~~initiation~~ if renal function is compromised**,** ~~or~~ there are toxicities related to the administration of the AVP**, or for any other medically indicated reason.**

In all subjects**,** plasma will be collected for central laboratory CMV viral load testing every two weeks from Day 100 through Day 200, then monthly through last study visit.

In cases where CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected from the first Study Drug injection through Day 395, a **sample for** ~~an additional central and local laboratory~~ CMV viral load will be collected at the time of the first CMV symptom recognition **and sent to a local and the central laboratory**.

CMV-specific anti-viral therapy (AVT) should be initiated for CMV disease and can be initiated for CMV viremia based on the central or local laboratory results and standard of care.

If CMV-specific AVT is initiated, ~~both~~ a central ~~and a local~~ CMV viral load will be obtained at a minimum of weekly from the time CMV-specific AVT is initiated until discontinuation.

In addition, each time a local CMV viral load sample is collected, a plasma sample will also be collected and sent to the central laboratory for CMV viral load testing.

Subjects will be followed for one year post first Study Drug injection (Study completion/Day 395) for CMV viremia, CMV syndrome, CMV tissue-invasive disease, ~~and~~ CMV-specific AVT, graft survival, ~~creatinine~~ and subject survival ~~through the Study Completion/Day 395 Visit~~.

Subjects will be followed for one year post first Study Drug injection for resistance to valganciclovir or ganciclovir.

Viral resistance will be **assessed by a Central lab when there is no reduction in** ~~measured~~

~~if the~~ viral load ~~has not decreased~~
two weeks after initiating **valganciclovir/ ganciclovir,** ~~CMV specific AVT or~~ when there is no improvement in clinical signs and symptoms two weeks after initiating valganciclovir or ganciclovir ~~for CMV viremia and/or disease~~ **or any time it is clinically indicated.**

Immunogenicity to pp65 and gB will be assessed prior to Dose 1, two weeks after Dose 2, prior to Dose 3, two weeks after Dose 4, prior to Dose 5 and at the last study visit.

Subjects will be evaluated for local and systemic reactogenicity **15 minutes and** one hour after each Study Drug injection and for 7 days by subject reporting via diary after each Study Drug injection. All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post first Study Drug injection.

Subjects will be contacted by telephone ~~annually at~~ 6 months after Day 395, then annually for the next 4 years, to evaluate long-term safety related to the deoxyribonucleic acid (DNA) vaccine. Mortality, development of any new malignancies, development of infection requiring hospitalization or resulting in death, graft survival, creatinine and erythema and/or induration at the injection sites will be assessed by questionnaire and available patient records.

IV. Synopsis, Inclusion Criteria
Page 19
WAS:
5. Subject started valganciclovir or ganciclovir within 10 days of transplant and has received it up to the time of Randomization.
IS AMENDED TO:
5. Subject started valganciclovir or ganciclovir within 10 days of transplant and has received it **through** ~~up to the time of~~ Randomization**, per regulatory label (package insert)**.

IV. Synopsis, Exclusion Criteria **3.3 Exclusion Criteria**
Page 19 *Page 43*
ADDED:
5. **The subject requires dialysis on the day of Randomization.**

IV. Synopsis, Exclusion Criteria **3.3 Exclusion Criteria**
Page 20 *Page 43*
DELETED:
8. ~~Subject has had an episode of hyper acute or acute rejection prior to Randomization.~~

IV. Synopsis, Exclusion Criteria
3.3 Exclusion Criteria

Page 20; Exclusion # 9
Page 44

WAS:

9. Subject has received any of the following substances or treatments:
    a. Investigational research products within 28 days or 5 half lives whichever is longer, prior to Transplantation, or subject is scheduled to receive investigational research products through one year after Randomization.
    b. Alemtuzumab within 90 days prior to Randomization or is scheduled to receive alemtuzumab any time through one year post Randomization.
    c. Rituximab within 120 days prior to Randomization or is scheduled to receive rituximab any time through one year post Randomization.
    d. Live attenuated vaccines within one month (30 days) prior to the first dose of Study Drug or is scheduled to receive live attenuated vaccines within one month of any Study Drug injection.
    e. Subunit or killed vaccines within 14 days prior to the first dose of Study Drug or is scheduled to receive a subunit or killed vaccine within 14 days prior to any Study Drug injection.
    f. Administration of a CMV vaccine, including any prior exposure to ASP0113.
    g. Subject has received the following anti-viral therapies or it is planned for them to receive the AVT for prophylaxis of viral infections in excess of the following doses from time of transplant through Randomization:
        - *Aciclovir:* 1600 mg orally (total daily dose), or 500 mg/m^2/dose Intravenous (IV) (total daily dose)
        - *Valaciclovir:* 1000 mg orally (total daily dose)
        - *Famciclovir:* 500 mg orally (total daily dose)

IS AMENDED TO:

9. Subject has received any of the following substances or treatments:
    a. Investigational research products within 28 days or 5 half lives whichever is longer, prior to Transplantation, or subject is scheduled to receive investigational research products through one year after Randomization.
    b. Alemtuzumab within 90 days prior to Randomization or is scheduled to receive alemtuzumab any time through one year post Randomization.
    c. Rituximab within 120 days prior to Randomization or is scheduled to receive rituximab any time through one year post Randomization.
    d. **Eculizumab or bortezomib from the Day of Transplantation through the Day of Randomization or is scheduled to receive eculizumab or bortezomib any time through one year post Randomization.**
    e. **IVIG and/or plasmapheresis from Day of Transplant through Day of Randomization.**
    f. Live attenuated vaccines within one month (30 days) prior to the first dose of Study Drug or is scheduled to receive live attenuated vaccines within one month of any Study Drug injection.

g. Subunit or killed vaccines within 14 days prior to the first dose of Study Drug or is scheduled to receive a subunit or killed vaccine within 14 days prior to any Study Drug injection.
h. Administration of a CMV vaccine, including any prior exposure to ASP0113.
i. Subject has received the following anti-viral therapies or it is planned for them to receive the AVT for prophylaxis of viral infections in excess of the following doses from time of transplant through Randomization:
   - *Aciclovir:* 1600 mg orally (total daily dose), or 500 mg/m^2/dose Intravenous (IV) (total daily dose)
   - *Valaciclovir:* 1000 mg orally (total daily dose)
   - *Famciclovir:* 500 mg orally (total daily dose)

IV. Synopsis, Exclusion Criteria **3.3 Exclusion Criteria**
Page 20 *Page 44*
WAS:
11. Subject has any contraindication to valganciclovir or ganciclovir including, but not limited to, renal dysfunction or cytopenias on the Day of Randomization.
IS AMENDED TO:
11. Subject has any contraindication to **or cannot be dosed with** valganciclovir or ganciclovir **per package insert** ~~including, but not limited to, renal dysfunction or cytopenias~~ on the Day of Randomization **for any reason**.

IV. Synopsis, Exclusion Criteria **3.3 Exclusion Criteria**
Page 20 *Page 44*
WAS:
12. Subject has any contraindication to an intramuscular injection.
IS AMENDED TO:
12. Subject has, **or is expected to have during the Primary Study Period, a** ~~any~~ contraindication to an intramuscular injection.

IV. Synopsis, Exclusion Criteria
Page 20
WAS:
13. Subject has an Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) greater than 3 x Upper Limits of Normal (ULN) or total bilirubin greater than 2 x ULN unless secondary to suspected Gilbert's disease at Screening.

IS AMENDED TO:
13. Subject **within 3 days prior to Randomization,** has an Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) greater than 3 x Upper Limits of Normal (ULN) or total bilirubin greater than 2 x ULN unless secondary to suspected Gilbert's disease ~~at Screening~~.

IV. Synopsis; Concomitant Medication Restrictions or Requirements
Page 21; CMV Prophylaxis
WAS:
Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) continuously until day of Randomization to prevent CMV disease. Subjects will then receive CMV-specific AVP until 100 days post transplant. Subjects can have CMV-specific AVP interrupted or dose adjusted per standard of care after initiation if renal function is compromised or there are toxicities related to the administration of the AVP.
IS AMENDED TO:
Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) **through** ~~continuously until day of~~ Randomization to prevent CMV disease. **(The subject can miss up to two doses of valganciclovir or ganciclovir during this time period for any reason).** Subjects will then receive CMV-specific AVP **with valganciclovir or ganciclovir** until 100 days post transplant. Subjects can have **valganciclovir or ganciclovir** ~~CMV-specific AVP~~ interrupted**,** ~~or~~ dose adjusted **or replaced by other CMV-specific AVP** per standard of care after **the Day of Randomization** ~~initiation~~ if renal function is compromised**,** ~~or~~ there are toxicities related to the administration of the AVP**, or for any other medically indicated reason**.

IV. Synopsis; Concomitant Medication Restrictions or Requirements **5.1.4.2 *Pneumocystis jiroveci Pneumonia Prophylaxis***
Page 21; Pneumocystis jiroveci Pneumonia Prophylaxis *Page 50 ; 1st paragraph*
WAS:
Pneumocystis jiroveci pneumonia prophylaxis must be administered to all study participants according to the site's standard of practise and applied uniformly to all enrolled subjects. If there is no prophylactic Pneumocystis protocol, the investigator must decide on appropriate *Pneumocystis jiroveci* pneumonia prophylaxis.
IS AMENDED TO:
Pneumocystis jiroveci pneumonia prophylaxis must be **initiated for** ~~administered to~~ all study participants according to the site's standard **practice for kidney transplant recipients** ~~of practice~~ and applied uniformly to all enrolled subjects. **Dose may be adjusted or therapy interrupted for renal dysfunction, adverse events related to the administration of the therapy or for other clinically indicated reasons.** If there is no prophylactic Pneumocystis

protocol, the investigator must decide on appropriate *Pneumocystis jiroveci* pneumonia prophylaxis.

IV. Synopsis; Concomitant Medication Restrictions or Requirements
Page 22 ; Prohibited Concomitant Medications (Drugs or Therapies), bullet points 1- 3
WAS:
• Investigational research products through completion of Day 395 visit (Visit 13). • Alemtuzumab through completion of the study (Day 395 visit/Visit 13). Rituximab through completion of the study (Day 395 visit/Visit 13) except for Post-Transplant Lymphoproliferative Disorder.
IS AMENDED TO:
• Investigational research products through completion of Day 395 visit (Visit 13). • ~~Alemtuzumab through completion of the study (Day 395 visit /Visit 13).~~ • ~~Rituximab through completion of the study (Day 395 visit /Visit 13) except for Post-Transplant Lymphoproliferative Disorder.~~ • **Planned alemtuzumab and, anti-CD20 antibodies (including rituximab) eculizumab or bortezomib are not allowed from the Day of Randomization through the Primary Study Period (Day 395). These treatments may be given after the Day of Randomization if clinically indicated.**

IV Synopsis; Discontinuation Criteria
Page 22; Study and Treatment Discontinuation
WAS:
Subjects will be withdrawn from study treatment and will only be followed for mortality through public records if the following occurs: Withdrawal of consent by the subject.
IS AMENDED TO:
Subjects will be withdrawn from **investigational** study treatment **and all follow up assessments** and will only be followed for mortality through public records if the following occurs: Withdrawal of consent by the subject.

IV Synopsis; Discontinuation Criteria
Page 22; Treatment Only Discontinuation
WAS:
Treatment Only Discontinuation Subjects should continue to be followed according to the study Schedule of Assessments and Long Term Follow-up Schedule of Assessments, except post-dose Day 14 safety and laboratory and reactogenicity assessments/visits for those doses not given, but will be

withdrawn from study treatment if any of the following occur:

- Investigator's decision that further treatment is not in the best interest of the subject.
- Graft failure
- Pregnancy (female subjects only).
- Local reactogenicity with a grade ≥ 3 based on the criteria defined in appendices.
- Systemic reactogenicity for any grade ≥ 3 fever or any other grade 4 systemic reaction within one week of vaccination.

IS AMENDED TO:

Subjects should continue to be followed according to the study Schedule of Assessments and Long Term Follow-up Schedule of Assessments, except post-dose Day 14 safety and laboratory and reactogenicity assessments/visits for those doses not given, but will be withdrawn from **investigational** study treatment if any of the following occur:

- Investigator's decision that further treatment is not in the best interest of the subject.
- Graft failure
- Pregnancy (female subjects only).
- Local reactogenicity with a grade ≥ 3 based on the criteria defined in appendices **and confirmed by a health care professional.**
- Systemic reactogenicity for any grade ≥ 3 fever or any other grade 4 systemic reaction within one week of vaccination **and confirmed by a health care professional.**
- **Anaphylaxis Grade ≥ 3 per NCI ver. 4.03 criteria.**

IV. Synopsis; Endpoints for Evaluation

Page 22; Primary Efficacy

WAS:

Incidence of CMV viremia (defined as plasma viral load of ≥ 250 IU/mL by central assay) through one year post first Study Drug injection.

IS AMENDED TO:

Incidence of CMV viremia (defined as plasma viral load of ≥ **1000**~~250~~ IU/mL by central assay) through one year post first Study Drug injection.

IV. Synopsis; Endpoints for Evaluation

Page 23; Exploratory Efficacy

WAS:

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ 250 IU/mL by central assay) through one year post study first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.

- Number of episodes of CMV viral load of ≥ 250 IU/mL by central assay through one year
  post first Study Drug injection.
- Peak CMV viral load through one year post first Study Drug injection.
- Total CMV viral load through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV- associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of viral resistance to ganciclovir or valganciclovir through one year post first Study Drug injection as determined by a central laboratory assay.
- Incidence of biopsy-proven acute rejection (BPAR) through one year post first Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at month 13 calculated using the 4 variable Modification of Diet in Renal Disease (MDRD) formula.
- Incidence of clinically treated acute graft rejection through one year post first Study Drug injection.
- Health economic and outcomes research (HEOR).
- Patient-reported outcomes through one year post first Study Drug injection:
  - EuroQol-5 dimensions 5 levels (EQ-5D)
  - Kidney Transplant Questionnaire (KTQ)
  - Short Form Health Survey version 2 (SF-12v2)
- Healthcare resource utilization through one year post first Study Drug injection:

Resource use will be collected including the following: concomitant medications and procedures, hospitalizations, nonscheduled outpatient/clinic visits, emergency room visits, skilled nursing facility care, and hospice care.

IS AMENDED TO:

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ ~~250~~**1000** IU/mL by central assay) through one year post study first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of CMV viral load of ≥ ~~250~~**1000** IU/mL by central assay through one year
  post first Study Drug injection.
- Peak CMV viral load through one year post first Study Drug injection.
- ~~Total CMV~~ **Viral load area under the curve (AUC), as a measure of "cumulative** viral load**"** through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV- associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of viral resistance to ganciclovir or valganciclovir through one year

post first Study Drug injection as determined by a central laboratory assay.

- Incidence of biopsy-proven ~~acute~~**(T or B cell)** rejection (BPAR) (**Banff 2007 Grade ≥ 1**) through one year post first Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at ~~month 13~~the last study visit, calculated using the 4 variable MDRD formula.
- Incidence of clinically treated acute graft rejection through one year post first Study Drug injection.
- ~~Health economic and outcomes research (HEOR).~~
- Patient-reported outcomes through one year post first Study Drug injection:
  - EuroQol-5 dimensions 5 levels (EQ-5D)
  - Kidney Transplant Questionnaire (KTQ)
  - Short Form Health Survey version 2 (SF-12v2)
- Healthcare resource utilization through one year post first Study Drug injection:

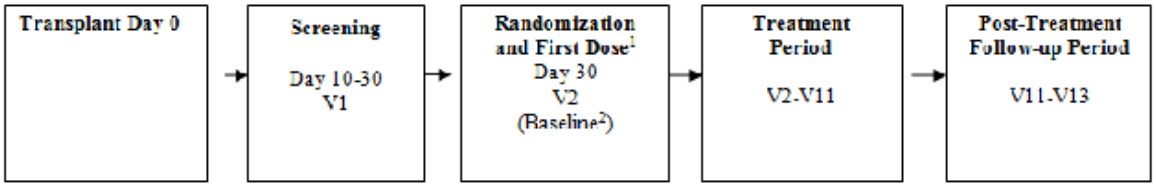
Resource use will be collected including the following: ~~concomitant medications and procedures,~~ .hospitalizations~~, nonscheduled outpatient/clinic visits,~~ **recorded as number of days in the Intensive Care Unit, Step-down Unit, and general medical ward, (including** emergency room visits~~, skilled nursing facility care,~~ **greater than 24 hours**), also non **-protocol -related physician visits** and ~~hospice care~~ **emergency room visits of. less than 24 hours.**

V. Flow Chart and Schedule of Assessments

Page 26; Flow Chart

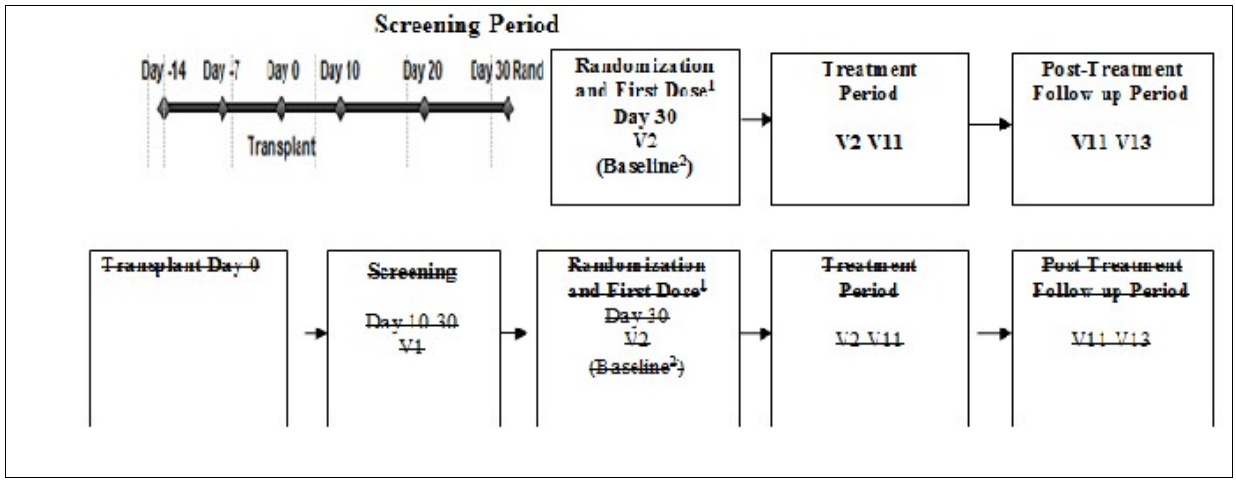
WAS:

Screening/Informed Consent through Visit 13/Day 395



IS AMENDED TO:

Screening/Informed Consent through Visit 13/Day 395


Screening Period
Day -14
Day -7
Day 0
Day 10
Day 20
Day 30 Rand
Transplant
Randomization and First Dose[1] Day 30 V2 (Baseline[2])
Treatment Period V2 V11
Post-Treatment Follow up Period V11 V13
~~Transplant Day 0~~
~~Screening Day 10 30 V1~~
~~Randomization and First Dose[1] Day 30 V2 (Baseline[2])~~
~~Treatment Period V2 V11~~
~~Post-Treatment Follow up Period V11 V13~~

V. Flow Chart and Schedule of Assessments, Table 1: Schedule of Assessments

Page 27

WAS:

	Day of Transplant[1]	Screening[15]	Randomization and		Dose 2		Dose 3		Day 100	Dose 4		Dose 5			Study Completion/ Early Termination[23]
Visit Number		1	2	3*	4	5	6	7*		8	9	10	11*	12	13
Day (From Transplant for dosing visits or prior dose)	0	10-30	30	14 days after Dose 1[25]	60	14 days after Dose 2[25]	90	14 days after Dose 3[25]		120	14 days after Dose 4[25]	180	14 days after Dose 5[25]	270	395
Visit Window (days)			+/-3	+/- 3	+/- 5	+/- 3	+/- 5	+/- 3		+/- 5	+/- 3	+/- 5	+/- 3	+/- 7	+14
Month	0		1		2		3			4		6		9	13
Valganciclovir/Ganciclovir[2]	→	→	→	→	→	→	→	→	→	→					
Informed Consent[3]		X													
Subject Number Assignment[4]		X													
Inclusion/Exclusion Assessment		X	X^P												
EQ-5D, KTQ, SF-12[5]			X^P		X^P		X^P			X^P		X^P			X
Medical History & Demographics[6]		X													
Clinical Evaluation (Physical Exam & Vitals)[7]		X	X^P		X^P		X^P			X^P		X^P		X	X
Concomitant Medication Review (including immunosuppressants)[8]		X	X^P		X^P	X	X^P			X^P	X	X^P		X	X
Health Economic Assessment (HEA)		X	X^P		X^P		X^P			X^P		X^P		X	X
Clinical Laboratories[9]		X	X^P	X	X^P	X	X^P	X		X^P	X	X^P	X		X
Urinalysis, with Microscopic Evaluation		X	X	X	X	X	X	X		X	X	X	X		X
Pregnancy Test (females)[10]		X	X^P		X^P		X^P			X^P		X^P		X	X
CMV Serologies[11]		X													
Adverse Event and SAE Review[12]		X	X^P		X^P	X	X^P			X^P	X	X^P		X	X
Transplant Information[13, 14]		X													
Randomization[15]			X^P												
CMV Plasma Viral Load Testing (see Table 1a)[16, 17, 24]										Every 2 Weeks →				Monthly →	
CMV Genotypic Resistance Testing, when applicable[18, 24]				→	→	→	→	→	→	→	→	→	→	→	→
Immunology Lab[19, 24]			X^P			X	X^P				X	X^P			X
Pharmacogenomics (PGx) – (Optional)[20, 24]			X^P												
Study Drug injection[21]			X		X		X			X		X			
Local & Systemic Reactogenicity Assessment[22]			X		X		X			X		X			

Patient and Graft Survival															X

ISAMENDED TO:

	Screening[1]	Baseline Randomization and Dose 1		Dose 2		Dose 3		Day 100	Dose 4		Dose 5			Study Completion/ Early Termination[23]
Visit Number	1	2	3*	4	5	6	7*		8	9	10	11*	12	13
Day (From Transplant for dosing visits or prior dose)	-14 through +30 Day of Transplant = Day 0[2]	30	14 days after Dose 1[25]	60	14 days after Dose 2[25]	90	14 days after Dose 3[25]		120	14 days after Dose 4[25]	180	14 days after Dose 5[25]	270	395
Visit Window (days)		+/-3	+/- 3	+/- 5	+/- 3	+/- 5	+/- 3		+/- 5	+/- 3	+/-5	+/- 3	+/- 10	+14
Month		1		2		3			4		6		9	13
Valganciclovir/Ganciclovir[3]	By Day 10 Post Transplant →													
Informed Consent[4]	X													
Subject Number Assignment[5]	X													
Inclusion/Exclusion Assessment	X	X^P												
EQ-5D, KTQ, SF-12[6]		X^P		X^P		X^P			X^P		X^P			X
Medical History & Demographics[7]	X													
Clinical Evaluation (Physical Exam & Vitals)[8]	X	X^P		X^P		X^P			X^P		X^P		X	X
Concomitant Medication Review (including immunosuppressants)[9]	X	X^P		X^P	X	X^P			X^P	X	X^P		X	X
Health Economic Assessment (HEA)	X	X^P		X^P		X^P			X^P		X^P		X	X
Clinical Laboratories[10]	X	X^P	X	X^P	X	X^P	X		X^P	X	X^P	X		X
Urinalysis, with Microscopic Evaluation	X	X^P	X	X^P	X	X^P	X		X^P	X	X^P	X		X
Urine:Protein Creatinine Ratio	X	X^P	X	X^P	X	X^P	X		X^P	X	X^P	X		X
Pregnancy Test (females)[11]	X	X^P		X^P		X^P			X^P		X^P		X	X
CMV Serologies[12]	X													
Adverse Event and SAE Review[13]	X	X^P		X^P	X	X^P			X^P	X	X^P		X	X
Transplant Information[14, 15]		X												
Randomization[1]		X^P												
CMV Plasma Viral Load Testing (see Table 1a)[16, 17, 24]								Every 2 Weeks →					Monthly →	
CMV Genotypic Resistance Testing, when applicable[18, 24]			→											
Immunology Lab[19, 24]		X^P			X	X^P				X	X^P			X
Pharmacogenomics (PGx) – (Optional)[20, 24]		X^P												
Study Drug injection[21]		X		X		X			X		X			

Local & Systemic Reactogenicity Assessment[22]		X		X		X			X		X			
Patient and Graft Survival														X

V. Flow Chart and Schedule of Assessments, Table 1a: Plasma Viral Load Schedule

Page 28

WAS:

	Every Other Week								Monthly						
	Day 100*	Day 114	Day 128 *	Day 142*	Day 156*	Day 170*	Day 184	Day 198*	Day 230*	Day 260	Day 290*	Day 320*	Day 350*	Day 380*	Day 395
CMV Visit Window (days)	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5
May draw with Visit:	Visit 7*						Visit 10	Visit 11*		Visit 12					Visit 13
CMV Plasma Viral Load Testing[16, 17, 24]	X	X	X	X	X	X	X^P	X	X	X	X	X	X	X	X

ISAMENDED TO:

	Every Other Week								Monthly						
	Day 100*	Day 114*	Day 128*	Day 142*	Day 156*	Day 170*	Day 184	Day 198*	Day 230*	Day 260	Day 290*	Day 320*	Day 350*	Day 380*	Day 395
CMV Visit Window (days)	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-~~35~~	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+**14**/-5
CMV Window							**Day 179-189**	**Day 193-203**		**Day 255-267**					
Overlap with Regular Visit†							**Days 179-185**	**Days 191-197**		**Days 260-267**					**Days 395-409**
May draw with Visit:	Visit 7*						Visit 10	Visit 11*		Visit 12					Visit 13
CMV Plasma Viral Load Testing[16, 17, 24]	X	X	X	X	X	X	X^P	X	X	X	X	X	X	X	X

*** = Visit procedures may be performed by Home Health Care (HHC)). Viral load blood draws may be combined with Visits 10, 11 12 & 13 at the investigator site when they are scheduled to coincide within each visit's windows .**

† Days in Study Schedule when CMV and Regular Visit can be performed together per Protocol. The overlap used assumes the visits are done exactly on the specified visit day from Transplant. If +/- window is used for a dosing visit, the corresponding follow up visit should take place within the 14 days +/-3 from the date of the Study Drug dose. Visits 10 & 11 must be at least 7 days apart.

V. Flow Chart and Schedule of Assessments, Tables 1 and 2 Footnotes

Pages 29-30

WAS:

1. The date of transplant (day of skin closure) defines Day 0 and all visit days are relative to Day 0.
2. Subjects are to receive prophylactic valganciclovir or ganciclovir starting within 10 days post transplant through Randomization. Valganciclovir or ganciclovir dose is to be given per the package insert. The subject is to receive CMV-specific AVP until 100 days post transplant. Subjects can have CMV-specific AVP interrupted or dose adjusted per standard of care after first dose of Study Drug if renal function is compromised or there are toxicities related to the administration of the AVP.
3. Informed consent must be obtained prior to the performance of any study-related procedure and before Randomization.
4. Subjects will be assigned a subject number for use throughout the study at the Screening Visit via the Interactive Response Technology (IRT) system.
5. The EQ-5D, Kidney Transplant Questionnaire (KTQ) and the SF-12 v2, should be completed by the subject prior to any other study assessments or visit procedures. Subjects should complete these assessments in the following order: EQ-5D first, KTQ second, SF-12 last. For all three patient-reported outcome measures, i.e. EQ-5D, KTQ, SF-12, the answers must come from the subject. If the subject is unable to fill out the questionnaire, the assessment should not be performed. If the subject is unable to answer an individual question, the rest of the questionnaire should still be completed.
6. Medical history must include demographics, (age, gender, race), diagnosis for renal failure, length of time on dialysis, history of prior kidney transplant, and diabetes.
7. A complete physical examination (PE) will be conducted at the Screening, Baseline and the Study Completion/Day 395 Visit (V13). At all other visits where a PE is performed (Visits 4, 6, 8, 10 and 12); symptom-directed physical examinations may be done. The evaluations conducted at each visit are to be performed by the Investigator or qualified medical personnel who routinely perform these evaluations in this patient population. Vital signs will be collected immediately prior to Study Drug injection, at 15 minutes and 60 minutes post Study Drug injection. Vital signs include blood pressure, pulse rate, respiratory rate and temperature. Height will be collected at the Screening Visit only. Weight will be collected at V1 and at Study Completion/Day 395 (Visit 13). If Screening is done > 3 days prior to Randomization, the PE must be repeated at Randomization.
8. All concomitant medications and therapies administered from 10 days prior to transplant through the Study Completion Visit (Day 395/Visit 13) will be collected on the eCRF. Medications used for anesthesia will not be recorded.
9. Clinical laboratory samples will be drawn at Screening (Visit 1), before each Study Drug injection, at each follow-up time point for the injections, and at the last study visit. Clinical labs will be performed by a local laboratory and will include hematology, biochemistry, including a hepatic profile and urinalysis with microscopic evaluation. Screening clinical labs may be re drawn once if initial results would preclude Randomization and the Investigator feels out of range results were transient. Results will be entered into the eCRF.
10. For all females of childbearing potential, a urine pregnancy test will be performed at Screening, prior to each dose, at Visit 10, 12, and at the Study Completion/Day 395 Visit (Visit 13). All pregnancy tests will be done locally. For subjects who receive mycophenolate mofetil (MMF), additional pregnancy testing should be done in accordance with local requirements.
11. CMV serologies must have been performed within 8 weeks prior to transplant. If CMV serostatus is not available from this time period, CMV serostatus may be assessed at the Screening Visit with results available prior to Randomization.
12. AEs and SAEs will be collected from time of signing of informed consent through one year post Study Drug injection [Study Completion Day 395

Visit (Visit 13)].

13. Transplant information includes type of transplant (Living Related Donor, Living Unrelated Donor, or Deceased Donor).
14. Donor information includes donor demographics, (age, gender, race), viral serologies (CMV (required), HBV, HCV) EBV, (if available)), ABO blood group and HLA typing. (Recipient information includes ABO blood group, HLA typing, HLA cross match at time of transplant (as determined by the site's standard method of determination), and viral serologies (CMV (required), HBV, HCV and EBV, (if available)).
15. Screening and Randomization can take place on the same day as long as Clinical Labs are drawn and results are available on the day of Randomization. If Screening is done > 3 days prior to Randomization, Clinical Labs must be repeated at Randomization.
16. Plasma viral load by both the central and local laboratory will be routinely monitored every other week (+/-3 days) from Day 100 through Day 200, then monthly (+/- 5 days) until end of study. Plasma viral load by central and local laboratory will also be assessed for cause in case of suspect CMV disease and at least once a week from initiation of CMV-specific AVT until the course is completed.
17. Plasma viral load assessment results performed by the local laboratory will be reported on the eCRF. Local CMV plasma viral load testing may be performed only at a local laboratory approved by the Sponsor.
18. A plasma sample will be drawn and results will be reported for CMV genotypic resistance when there is viremia without a reduction in viral load after two weeks of treatment with valganciclovir and/or ganciclovir, or when clinical signs and symptoms have not improved two weeks after initiating or increasing valganciclovir and/or ganciclovir for CMV viremia or disease.
19. Immunogenicity laboratories include collection of blood for the gB antibody and pp65 T-cell assays. Samples should be drawn at Visits 2, 5, 6, 9, 10 and 13. Visits 2, 6 and 10 are Study Drug injection visits and blood sampling will be collected prior to the Study Drug injection. Samples for T-cell assays will not be collected if the Absolute Lymphocyte Count (ALC) is known to be ≤ 500 mm^3 by local or central laboratory measurement.
20. Subjects who consent to participate in the PGx sub study will have a whole blood sample collected during the Baseline Visit (Visit 2), after Randomization but prior to the first Study Drug injection.
21. A Study Drug injection should not be given if the subject has been on an anticoagulant within 5 half-lives prior to the injection. Low dose anticoagulants that are used for prevention of deep vein thrombosis are allowed.
22. Local reactogenicity and symptoms of systemic reactogenicity will be evaluated one hour after each injection and then for seven days after each injection by subject reporting via diary. After injection in the clinic, the subject must be in direct view of the clinic staff for 15 minutes following each injection, then remain in the clinic area for an additional 45 minutes for evaluation of local and systemic reactogenicity. Vital signs, including temperature, pulse, respiration and blood pressure will be collected just prior to injection, 15 minutes post Study Drug injection and at one hour post Study Drug injection.
23. The Study Completion/Day 395 Visit (Visit 13) must occur on Day 395 up through +14 days (between Day 395 to 379). For a subject who prematurely withdraws from the study (discontinues treatment with no continued follow-up), the Study Completion Visit should be completed within 14 days of study withdrawal.
24. Specimen drawn and sent to the Central Laboratory.
25. If a Study Drug dose is missed, the 14 day follow up clinical laboratory samples for hematology, biochemistry and hepatic profile should not be collected. Scheduled Immunogenicity Labs (Visit 5 & 9) must still be collected.

IS AMENDED TO:

1. **Screening may be done from Day -14 up to Randomization, Day 30. Screening and Randomization can take place on the same day as long as Clinical Labs are drawn and results are available on the day of Randomization. If Screening is done > 3 days prior to Randomization, Clinical Labs, urinalysis and urine protein: creatinine ratio must be repeated and available prior to Randomization. Subjects may be rescreened due to rescheduling of transplant surgery provided the screening procedures are repeated and fall within the -14 day to + 30-day window relative to the Day of Transplant. First study drug dosing must take place within 24 hours of Randomization.**
2. The date of transplant (day of skin closure) defines Day 0 and all visit days are relative to Day 0.
3. Subjects are to receive prophylactic valganciclovir or ganciclovir starting within 10 days post transplant through **the Day of** Randomization **to prevent CMV disease. (The subject can miss up to two doses of valganciclovir or ganciclovir during this time period for any reason).** Valganciclovir or ganciclovir dose is to be given per the package insert. The subject **will then continue** ~~is~~ to receive CMV-specific AVP until 100 days post transplant. Subjects can have CMV-specific AVP interrupted**,**~~or~~ dose adjusted **or replaced by other CMV-specific AVP** per standard of care after **the Day Randomization**~~first dose of Study Drug~~ if renal function is compromised**,** ~~or~~ there are toxicities related to the administration of the AVP**, or for any other medically indicated reason**.
4. Informed consent must be obtained prior to the performance of any study-related procedure~~ and before Randomization~~.
5. Subjects will be assigned a subject number for use throughout the study at the Screening Visit via the Interactive Response Technology (IRT) system.
6. The EQ-5D, Kidney Transplant Questionnaire (KTQ) and the SF-12 v2, should be completed by the subject prior to any other study assessments or visit procedures. Subjects should complete these assessments in the following order: EQ-5D first, KTQ second, SF-12 last. For all three patient-reported outcome measures, i.e. EQ-5D, KTQ, SF-12, the answers must come from the subject. If the subject is unable to fill out the questionnaire, the assessment should not be performed. If the subject is unable to answer an individual question, the rest of the questionnaire should still be completed.
7. Medical history must include demographics, (age, gender, race), diagnosis for renal failure, length of time on dialysis, history of prior kidney transplant, and diabetes.
8. A complete physical examination (PE) will be conducted at the Screening, Baseline and the Study Completion/Day 395 Visit (V13). At all other visits where a PE is performed (Visits 4, 6, 8, 10 and 12); symptom-directed physical examinations may be done. The evaluations conducted at each visit are to be performed by the Investigator or qualified medical personnel who routinely perform these evaluations in this patient population. Vital signs will be collected immediately prior to Study Drug injection, at 15 minutes and 60 minutes post Study Drug injection. Vital signs include blood pressure, pulse rate, respiratory rate and temperature. Height will be collected at the Screening Visit only. Weight will be collected at V1**, V2** and at Study Completion/Day 395 (Visit 13). If Screening is done > 3 days prior to Randomization, the PE must be repeated at Randomization.
9. All concomitant medications and therapies administered from **14**~~10~~ days prior to transplant through the Study Completion Visit (Day 395/Visit 13) will be collected on the eCRF. Medications used for anesthesia **during the transplant surgery** will not be recorded.
10. Clinical laboratory samples will be drawn at Screening (Visit 1), before each Study Drug injection, at each follow-up time point for the injections, and at the last study visit. Clinical labs will be performed by a local laboratory and will include hematology, biochemistry, including a hepatic profile**,** ~~and~~ urinalysis with microscopic evaluation **and urine protein: creatinine ratio**. Screening clinical labs may be re drawn once if initial results would preclude Randomization and the Investigator feels out of range results were transient. Results will be entered into the eCRF. **Safety labs (hematology, biochemistry, hepatic profile, urine protein: creatinine ratio and urinalysis) drawn by Home Health Care for Investigator sites utilizing this service will be analyzed by the Central Laboratory.**
11. For all females of childbearing potential, a urine pregnancy test will be performed at Screening, prior to each dose, at Visit 10, 12, and at the Study Completion/Day 395 Visit (Visit 13). All pregnancy tests will be done locally. For subjects who receive mycophenolate mofetil (MMF), additional

pregnancy testing should be done in accordance with local requirements.

12. CMV serologies must have been performed within 8 weeks prior to transplant. If CMV serostatus is not available from this time period, CMV serostatus may be assessed at the Screening Visit with results available prior to Randomization.
13. AEs and SAEs will be collected from time of signing of informed consent through one year post Study Drug injection [Study Completion Day 395 Visit (Visit 13)]. **AEs should be recorded as a change in medical status or medical history, from the time of signing of the informed consent until the first dose of study drug. SAEs from the time of signing the informed consent will be recorded on the SAE worksheet and reported per Section 5.5.6. AEs reported after the first dose will be reported on the AE eCRF. Note: The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.**
14. Transplant information includes type of transplant (Living Related Donor, Living Unrelated Donor, or Deceased Donor).
15. Donor information includes donor demographics~~,~~ (age, gender, race), viral serologies (CMV **[**required**]**,~~)~~ HBV, HCV, EBV, **[**if available**]; and HCV PCR RNA** [if available]),~~)~~ ABO blood group and HLA typing. Recipient information includes ABO blood group, HLA typing, HLA cross match at time of transplant (as determined by the site's standard method of determination), and viral serologies (CMV [required],~~),~~ HBV, HCV and EBV [if available], **and HCV PCR RNA** [**if available**]).

    ~~15. Screening and Randomization can take place on the same day as long as Clinical Labs are drawn and results are available on the day of Randomization. If Screening is done > 3 days prior to Randomization, Clinical Labs must be repeated at Randomization.~~
16. Plasma viral load by ~~both~~ the central ~~and local~~ laboratory will be routinely monitored every other week (+/-3 days) from Day 100 through Day 200, then monthly (+/- 5 days) until end of study. Plasma viral load by central and local laboratory will also be assessed for cause in case of suspect CMV disease and at least once a week **by Central lab** from initiation of CMV-specific AVT until the course is completed. **For cause CMV viral loads should be performed at a local lab approved by Astellas as Central lab viral load results may not be available in a timely manner to guide treatment decisions.**
17. Plasma viral load assessment results performed by the local laboratory will be reported on the eCRF. Local CMV plasma viral load testing may be performed only at a local laboratory approved by the Sponsor.
18. A plasma sample will be drawn **and sent to the central lab** and results will be reported for CMV genotypic resistance when there is viremia without a reduction in viral load after two weeks of treatment with valganciclovir and/or ganciclovir, or when clinical signs and symptoms have not improved two weeks after initiating or increasing valganciclovir and/or ganciclovir for CMV viremia or disease **or any time resistance to any CMV-specific ATV is suspected by the Investigator**.
19. Immunogenicity laboratories include collection of blood for the gB antibody and pp65 T-cell assays. Samples should be drawn at Visits 2, 5, 6, 9, 10 and 13. Visits 2, 6 and 10 are Study Drug injection visits and blood sampling will be collected prior to the Study Drug injection. Samples for T-cell assays will not be collected if the Absolute Lymphocyte Count (ALC) is known to be ≤ 500 mm^3 by local or central laboratory measurement.
20. Subjects who consent to participate in the PGx sub study will have a whole blood sample collected during the Baseline Visit (Visit 2), after Randomization but prior to the first Study Drug injection.
21. A Study Drug injection should not be given if the subject **1)** has been on an anticoagulant within 5 half-lives prior to the injection~~.~~ **(**Low dose anticoagulants that are used for prevention of deep vein thrombosis are allowed**) or 2) has a Temperature ≥ 100.4° F or 38° C (per NCI Grade 1)**.
22. Local reactogenicity and symptoms of systemic reactogenicity will be evaluated one hour after each injection and then for seven days after each injection by subject reporting via diary. After injection in the clinic, the subject must be in direct view of the clinic staff for 15 minutes following each injection, then remain in the clinic area for an additional 45 minutes for evaluation of local and systemic reactogenicity. Vital signs, including

temperature, pulse, respiration and blood pressure will be collected just prior to injection, 15 minutes post Study Drug injection and at one hour post Study Drug injection. **Using the pre-injection vital signs as baseline, if a post Study Drug injection vital sign meets Grade 1-4 criteria per Appendix 5, they are to be repeated and confirmed within 5 minutes of the first assessment.**

23. The Study Completion/Day 395 Visit (Visit 13) must occur on Day 395 up through +14 days (between Day 395 to 379). For a subject who prematurely withdraws from the study (discontinues treatment with no continued follow-up), the Study Completion Visit should be completed within 14 days of study withdrawal.
24. Specimen drawn and sent to the Central Laboratory.
25. If a Study Drug dose is missed, the 14 day follow up clinical laboratory samples for hematology, biochemistry**, urinalysis and urine protein: creatinine ratio** and hepatic profile should not be collected. Scheduled Immunogenicity Labs (Visit 5 & 9) must still be collected.

V. Flow Chart and Schedule of Assessments, Table 2, Schedule of Assessments – Long-term Follow-up Period
Page 31; footnotes
WAS:
Subjects will be contacted by telephone at 6 months after Day 395, then annually, for the next 4 years for long-term safety related to the DNA vaccine. Items to be assessed by questionnaire and via retrospective chart review of available medical records. *Creatinine values will be recorded if they have been collected within 3 months prior to the follow-up telephone contact and are included in the subject's available medical records.
IS AMENDED TO:
Subjects will be contacted by telephone at 6 months after Day 395, then annually, for the next 4 years for long-term safety related to the DNA vaccine. Items **are** to be assessed by questionnaire and via retrospective chart review of available medical records. **During the long-term follow-up period, if an SAE is identified and deemed possibly or probably related to the study medication, an SAE report on the SAE worksheet must be sent to the sponsor per Section 5.5.6.** *Creatinine values will be recorded if they have been collected within 3 months prior to the follow-up telephone contact and are included in the subject's available medical records.

2.2.1 Study Design
Page 37, 1st paragraph
WAS:
This is a randomized, double-blind, placebo-controlled trial which will enroll 140 CMV-seronegative recipients of kidney transplant from a CMV-seropositive donor at 80 clinical sites. Subjects will be randomized at Day 30 ±3, in relation to the day of transplant, in a 1:1 ratio to ASP0113 or placebo, and stratified by use of anti-thymocyte globulin (ATG) as induction therapy and by receipt of a kidney from a living or deceased donor. The active compound will be a vaccine (ASP0113) which contains two plasmids encoding gB and pp65 each at 2.5 mg/mL, formulated with CRL1005 poloxamer and benzalkonium chloride (BAK).
IS AMENDED TO:
This is a randomized, double-blind, placebo-controlled trial which will enroll 140 CMV-seronegative recipients of kidney transplant from a CMV-seropositive donor at 80 clinical sites. Subjects will be randomized at Day 30 ±3, in relation to the day of transplant, in a 1:1 ratio to ASP0113 or placebo, and stratified by use of anti-thymocyte globulin (ATG) ~~as induction therapy~~**prior to Randomization** and by receipt of a kidney from a living or deceased donor. The active compound will be a vaccine (ASP0113) which contains two plasmids encoding gB and pp65 each at 2.5 mg/mL, formulated with CRL1005 poloxamer and benzalkonium chloride (BAK).

2.2.1 Study Design
Page 38,4th and 5th paragraphs
WAS:
Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) continuously until the day of Randomization to prevent CMV disease. Subjects will then continue to receive prophylactic valganciclovir or ganciclovir (dose per package insert) to prevent CMV disease until 100 days post transplant. Subjects can have CMV-specific AVP interrupted or dose adjusted per standard of care after initiation if renal function is compromised or there are toxicities related to the administration of the AVP. In all subjects, plasma will be collected for central laboratory CMV viral load testing every two weeks from Day 100 through Day 200, then monthly through last Study visit Day 395. In cases where CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected from the first Study Drug injection through Day 395, an additional central and local CMV viral load sample will be collected at the time of the first CMV symptom recognition.
IS AMENDED TO:
Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) ~~continuously until~~**through** the day of Randomization to prevent CMV disease**. (The subject can miss up to two valganciclovir or ganciclovir doses during this time period for any reason).** Subjects will then continue to receive ~~prophylactic~~**CMV specific CMV AVP with** valganciclovir or ganciclovir (dose per package insert) to prevent CMV disease until 100 days post transplant. Subjects can have ~~CMV-specific AVP~~ **valganciclovir or ganciclovir** interrupted ~~or~~ **,**dose adjusted **or replaced by other CMV-specific AVP** per standard of care after ~~initiation~~**the day of Randomization** if renal function is compromised~~or~~**,** there are toxicities related to the administration of the AVP~~.~~ ,**or for any other medically indicated reason.** In all subjects, plasma will be collected for central laboratory CMV viral load testing every two weeks from Day 100 through Day 200, then monthly through last Study visit Day 395. In cases where CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected from the first Study Drug injection through Day 395, ~~an additional central and~~ **a** local CMV viral load sample will be collected at the time of the first CMV symptom recognition.

2.2.1 Study Design
Page 38, 6th paragraph
WAS:
Through Day 395, CMV-specific AVT should be initiated for CMV disease and can be initiated for CMV viremia based on the central or local laboratory results and standard of care at each institution. If CMV- specific AVT is initiated, a central and local CMV viral load will be obtained at a minimum of weekly from the time CMV- specific AVT is initiated until discontinuation.
IS AMENDED TO:

Through Day 395, CMV-specific AVT should be initiated for CMV disease and can be initiated for CMV viremia based on the central or local laboratory results and standard of care at each institution. If CMV- specific AVT is initiated, a central ~~and local~~ CMV viral load will be obtained at a minimum of weekly from the time CMV- specific AVT is initiated until discontinuation. **For cause CMV viral loads should be performed at a local lab approved by Astellas as Central lab viral load results will not be available in a timely manner to guide treatment decisions.**

2.2.1 Study Design
Pages 39: 11th and 12th paragraphs
WAS:
Subjects will be followed for one year after first Study Drug injection (Primary Study completion/Day 395) for CMV viremia, CMV syndrome, CMV tissue-invasive disease, CMV-specific AVT, graft survival, creatinine and subject survival through the Study Completion/Day 395 (Visit 13). Subjects will be followed for one year after the first Study Drug injection for resistance to valganciclovir or ganciclovir. Viral resistance will be measured if the viral load has not decreased 2 weeks after initiating CMV-specific AVT or when there is no improvement in clinical signs and symptoms two weeks after initiating valganciclovir and/or ganciclovir for CMV viremia and/or disease.
IS AMENDED TO:
Subjects will be followed for one year after first Study Drug injection (Primary Study completion/Day 395) for CMV viremia, CMV syndrome, CMV tissue-invasive disease, CMV-specific AVT, graft survival~~, creatinine~~ and subject survival ~~through the Study Completion/Day 395 (Visit 13)~~. Subjects will be followed for one year after the first Study Drug injection for resistance to valganciclovir or ganciclovir. Viral resistance will be ~~measured if~~ **assessed by a Central lab when** the viral load has not decreased 2 weeks after initiating ~~CMV specific AVT or~~**valganciclovir/ganciclovir,** when there is no improvement in clinical signs and symptoms two weeks after initiating valganciclovir ~~and/or~~ /ganciclovir ~~for~~**or any time resistance to any** CMV ~~viremia and/or disease~~**-specific AVT is suspected by the Investigator**.

2.2.1 Study Design
Pages 39: 16th paragraph
WAS:
All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post Study Drug injection. AEs and SAEs occurring from signing of informed consent until just prior to the first dose of Study Drug, should be reported as a change in medical status or medical history.
IS AMENDED TO:
All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing

of the informed consent through one year post Study Drug injection. AEs~~and SAEs~~ occurring from signing of informed consent until just prior to the first dose of Study Drug, should be reported as a change in medical status or medical history. **SAE's from the time of signing the informed consent will be recorded on the SAE worksheet and reported per Section 5.5.6.AE's reported after the first dose will be reported on the AE eCRF. The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.**

2.3.1 Primary Efficacy Endpoints
Page 40
WAS:
Incidence of first CMV viremia (defined as plasma viral load of ≥ 250 IU/mL by central assay) through one year post first Study Drug injection.
IS AMENDED TO:
Incidence of ~~first~~ CMV viremia (defined as plasma viral load of ≥ **1000**~~250~~ IU/mL by central assay) through one year post first Study Drug injection.

2.3.3 Exploratory Efficacy Endpoints
Page 40-41
WAS:
• Number of opportunistic infections other than CMV through one year post first Study Drug injection. • Time to first CMV viremia (defined as plasma viral load of ≥ 250 IU/mL by central assay) through one year post study first Study Drug injection. • Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection. • Number of episodes of CMV viral load of ≥ 250 IU/mL by central assay through one year post first Study Drug injection. • Peak CMV viral load through one year post first Study Drug injection. • Total CMV viral load through one year post first Study Drug injection. • Number of episodes of adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection. • Number of episodes of viral resistance to ganciclovir or valganciclovir through one year post first Study Drug injection as determined by a central laboratory assay. • Incidence of biopsy-proven acute rejection (BPAR) through one year post first Study Drug injection. • Estimated glomerular filtration rate (eGFR) at the last study visit calculated using the 4 variable MDRD formula. • Incidence of clinically treated acute graft rejection through one year post first Study Drug injection.

- Health economic and outcomes research (HEOR).
- Patient-reported outcomes through one year post first Study Drug injection.
    - EuroQol-5 dimensions 5 levels (EQ-5D)
    - Kidney Transplant Questionnaire (KTQ)
    - Short Form Health Survey version 2 (SF-12v2)
- Healthcare resource utilization through one year post first Study Drug injection.

Resource use will be collected including the following: concomitant medications and procedures, hospitalizations, nonscheduled outpatient/clinic visits, emergency room visits, skilled nursing facility care, and hospice care.

IS AMENDED TO:

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ ~~250~~**1000** IU/mL by central assay) through one year post study first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of CMV viral load of ≥ ~~250~~**1000** IU/mL by central assay through one year post first Study Drug injection.
- Peak CMV viral load **and area under the curve (AUC)** through one year post first Study Drug injection.
- **Viral load area under the curve (AUC), as a measure of "cumulative** ~~Total CMV~~ viral load**"** through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of viral resistance to ganciclovir or valganciclovir through one year post first Study Drug injection as determined by a central laboratory assay.
- Incidence of biopsy-proven ~~acute~~**(T or B cell)** rejection (BPAR)**(Banff 2007 Grade ≥ 1)** through one year post first Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at the last study visit ~~month 13~~ calculated using the 4 variable MDRD formula.
- Incidence of clinically treated acute graft rejection through one year post first Study Drug injection.
- ~~Health economic and outcomes research (HEOR).~~
- Patient-reported outcomes through one year post first Study Drug injection.
    - EuroQol-5 dimensions 5 levels (EQ-5D)
    - Kidney Transplant Questionnaire (KTQ)
    - Short Form Health Survey version 2 (SF-12v2)
- Healthcare resource utilization through one year post first Study Drug injection.

Resource use will be collected including the following: ~~concomitant medications and procedures,~~ hospitalizations~~, nonscheduled outpatient/clinic visits,~~ **recorded as number of**

days in the Intensive Care Unit, Step-down Unit, and general medical ward (including emergency room **visits greater than 24 hours), also non -protocol -related physician visits and emergency room** visits~~, skilled nursing facility care, and hospice care.~~ **of less than 24 hours.**

3.2 Inclusion Criteria
Page 42
WAS:
5. Subject started valganciclovir or ganciclovir (dose per package insert) within 10 days of transplant and has received it up to the time of Randomization.
IS AMENDED TO:
5. Subject started valganciclovir or ganciclovir ~~(dose per package insert)~~ within 10 days of transplant and has received it **through** ~~up to the time of~~ Randomization**, per regulatory label (package insert)**.

3.3 Exclusion Criteria
Page 44
WAS:
13. Subject has an AST or ALT greater than 3 x ULN or total bilirubin greater than 2 x ULN unless secondary to suspected Gilbert's disease at Screening.
IS AMENDED TO:
13. Subject**, within 3 days prior to Randomization,** has an AST or ALT greater than 3 x ULN or total bilirubin greater than 2 x ULN unless secondary to suspected Gilbert's disease ~~at Screening~~.

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)
Page 48
WAS:
One (1) mL of 5 mg/mL ASP0113 or placebo will be administered to the subjects at the clinical site via injection in the deltoid muscle, alternating sides with each dose, if possible. Preparation of Study Drug will be described in the Pharmacy Manual for the study. The syringes will be masked to maintain the study blind.
IS AMENDED TO:
One (1) mL of 5 mg/mL ASP0113 or placebo will be administered to the subjects at the clinical site via injection in the deltoid muscle, alternating sides with each dose, if possible. Preparation of Study Drug will be described in the Pharmacy Manual for the study. The syringes will be masked **as described in the Pharmacy Manual** to maintain the study blind.

5.1.1 Dose/Dose Regimen and Administration Period
Page 49, last paragraph, 1st sentence
WAS:
An injection should not be given if the subject has been on an anticoagulant within 5 half-lives prior to the injection or there is any other contraindication to an intramuscular injection.
IS AMENDED TO:
An injection should not be given if, **1)** the subject has been on an anticoagulant within 5 half-lives prior to the injection or there is any other contraindication to an intramuscular injection **or 2) has a Temperature ≥ 100.4° F or 38° C (per NCI Grade 1)**.

5.1.3 CMV Prophylactic Therapy
Page 49
WAS:
Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) continuously until day of Randomization to prevent CMV disease. Subjects will then receive CMV-specific AVP until 100 days post transplant. Subjects can have CMV-specific AVP interrupted per standard of care after initiation, if renal function is compromised or there are toxicities related to the AVP.
IS AMENDED TO:
Starting within 10 days of transplant, subjects will have received prophylactic valganciclovir or ganciclovir (dose per package insert) **through**~~continuously until day of~~ Randomization to prevent CMV disease. **(The subject can miss up to two valganciclovir or ganciclovir doses during this time period for any reason). After Randomization, subjects** ~~Subjects~~ will then receive CMV-specific AVP until 100 days post transplant. Subjects can have CMV-specific AVP interrupted**, dose adjusted or replaced by other CMV-specific AVP** per standard of care after **the day of Randomization,** ~~initiation,~~ if renal function is compromised**,** ~~or~~ there are toxicities related to the **administration of the AVP or for any other medically indicated reason** ~~AVP~~.

5.1.4.3 Prohibited Concomitant Medication
Page 50, bullet points 1-3
WAS:
• Investigational research products through completion of Day 395 visit (Visit 13). • Alemtuzumab through completion of the Day 395 visit (Visit 13). • Rituximab through completion of the Day 395 visit (Visit 13) except for Post-Transplant Lymphoproliferative Disorder (PTLD).
IS AMENDED TO:
• Investigational research products through completion of Day 395 visit (Visit 13).

- ~~Alemtuzumab through completion of the Day 395 visit (Visit 13).~~
- ~~Rituximab through completion of the Day 395 visit (Visit 13) except for Post-Transplant Lymphoproliferative Disorder (PTLD).~~
- **Planned alemtuzumab and, anti-CD20 antibodies (including rituximab) eculizumab or bortezomib are not allowed from the Day of Randomization through the Primary Study Period (Day 395). These treatments may be given after the Day of Randomization if clinically indicated.**

5.1.4.4 Concomitant Medication (Drugs and Therapies)
Page50
WAS:
All concomitant medications, immunosuppressive agents and therapies administered from 10 days prior to transplant through the Primary Treatment Period (Visit 13/Day 395) will be recorded at each study visit on the eCRF. Subjects should be instructed not to take any new medications or change the dose and frequency of their ongoing medications throughout the study period without consulting the investigator. Medications used for anesthesia purposes will not be recorded.
IS AMENDED TO:
All concomitant medications, immunosuppressive agents and therapies administered from **14**~~10~~ days prior to transplant through the Primary Treatment Period (Visit 13/Day 395) will be recorded at each study visit on the eCRF. Subjects should be instructed not to take any new medications or change the dose and frequency of their ongoing medications throughout the study period without consulting the investigator. Medications used for anesthesia purposes **during the transplant** will not be recorded.

5.2.4 Donor Information
Page 51
WAS
Demographics, (age, gender, race) Viral Serologies (CMV required, HBV, HCV, EBV, if available) ABO blood group HLA typing
IS AMENDED TO:
Demographics, (age, gender, race) Viral Serologies**;** ~~(~~CMV **(**required), HBV, HCV, EBV **(if available) and HCV PCR RNA,** (if available) ABO blood group HLA typing

5.2.5 Recipient Information
Page 51
WAS
ABO blood group HLA typing HLA cross match at time of transplant (as determined by the site's standard method of determination) Viral Serologies (CMV required, HBV, HCV, EBV, if available)
IS AMENDED TO:
ABO blood group HLA typing HLA cross match at time of transplant (as determined by the site's standard method of determination) Viral Serologies ~~(~~CMV **(**required**),** HBV, HCV, EBV~~,~~ **(**if available**), and HCV PCR RNA, (**if available**)**

5.3.3 Exploratory Efficacy Assessments
Page 52; 6th bullet point
WAS
● eGFR at Month 13/Day 395
IS AMENDED TO:
● eGFR at ~~Month 13/Day 395~~ **the last study visit**

5.3.4.4 Health Economic Assessment (HEA)
Page 54
WAS
Health Economic Assessments will include the following: concomitant medications and procedures, hospitalizations, nonscheduled clinic visits, emergency room visits, skilled nursing facility care, and hospice care. The information will be collected by the site via a retrospective review of the subject's medical record. HEA data will include both data being routinely captured for the subject (e.g., concomitant medications) as well as data that will be used specifically for these analyses (e.g., information on hospitalizations) (Appendix 18).
IS AMENDED TO:
Health Economic Assessments will include the following: ~~concomitant medications and procedures,~~ hospitalizations~~, nonscheduled clinic visits,~~ **recorded as number of days in the Intensive Care Unit, Step-down Unit, and general medical ward, (including** emergency room visits~~, skilled nursing facility care,~~ **greater than 24 hours) also non-protocol- related physician visits** and ~~hospice care.~~**emergency room visits less than 24 hours.** The information will be collected by the site via a retrospective review of the subject's medical record. HEA data will include both data being routinely captured for the subject (e.g.,

concomitant medications) as well as data that will be used specifically for these analyses (e.g., information on hospitalizations) (Appendix 18).

5.4.1 Vital Signs

Page 54

WAS:

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature) will be collected at all dosing visits, and at Screening (V1), and at V12 and 13. Height will be collected at Screening only. Weight will be collected at V1 and Study Completion (V13).

IS AMENDED TO:

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature) will be collected at all dosing visits, and at Screening (V1), and at V12 and 13. Height will be collected at Screening only. Weight will be collected at V1**, V2** and Study Completion (V13).

5.4.2 Adverse Events

Page 55, 2nd paragraph

WAS

All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post Study Drug injection. AEs and SAEs should be reported as a change in medical status or medical history from time of signing of informed consent through first dose of Study Drug.

IS AMENDED TO:

All adverse events (AEs) and serious adverse events (SAEs) will be collected from signing of the informed consent through one year post Study Drug injection**. AEs from the time of signing of informed consent through first dose of Study Drug should be captured on the medical history eCRF. If the AE is deemed possibly or probably related to Study Procedures prior to the first Study Drug injection, it will be recorded on the AE eCRF page. SAEs that occur from the signing of the informed consent form will be reported as per Section 5.5 and captured on the AE eCRF page. AEs and SAEs after the first dose of Study Drug should be captured on the AE eCRF page.** ~~AEs and SAEs should be reported as a change in medical status or medical history from time of signing of informed consent through first dose of Study Drug.~~

5.4.4 Systemic Reactogenicity Assessments

Page 55-56

WAS:

Specific signs of systemic reactogenicity will be evaluated one hour after each injection (Appendix 5). The subject must be in direct view of the clinic staff for 15 minutes following each injection, then remain in the clinic area for an additional 45 minutes for evaluation of

systemic reactogenicity. Vital signs, including temperature, pulse, respiration and blood pressure will be collected just prior to injection, 15 minutes post-injection and at one hour post-injection. Systemic measurements that will be followed for 7 days are fever, fatigue and myalgia.
WAS AMENDED TO:
Specific signs of systemic reactogenicity will be evaluated one hour after each injection (Appendix 5). The subject must be in direct view of the clinic staff for 15 minutes following each injection, then remain in the clinic area for an additional 45 minutes for evaluation of systemic reactogenicity. Vital signs, including temperature, pulse, respiration and blood pressure will be collected just prior to injection, 15 minutes post-injection and at one hour post-injection. **Using the pre-injection vital signs as baseline, if a post Study Drug injection vital sign meets Grade 1-4 criteria per Appendix 5, it is to be repeated and confirmed within 5 minutes of first assessment.** Systemic measurements that will be followed for 7 days are fever, fatigue and myalgia.

5.4.5 Laboratory Assessments
Page 56, 3rd bullet point
WAS
• Local laboratory values for CMV viral load should be collected and documented in the eCRF for subjects whenever AVT for CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected within the first 12 months post first Study Drug injection, when CMV-specific AVT is initiated and at a minimum of weekly from the time CMV specific AVT is initiated until discontinuation.
IS AMENDED TO:
• Local laboratory values for CMV viral load should be collected and documented in the eCRF for subjects whenever ~~AVT for~~ CMV disease (CMV syndrome or CMV tissue-invasive disease) is suspected within the first 12 months post first Study Drug injection **and**~~,~~ when CMV-specific AVT is initiated ~~and at a minimum of weekly from the time CMV specific AVT is initiated until discontinuation~~.

5.4.5 Laboratory Assessments
Page 56, 4th bullet point
ADDED:
• **If CMV AVT is initiated, Central lab CMV viral loads will be collected at a minimum of weekly from the time CMV specific AVT is initiated until discontinuation. Note: Central Lab turnaround time is estimated to be at least 3 days from receipt at the Central lab, not including holidays. If treatment decisions need to be made a local CMV viral load should be collected and analyzed at an Astellas approved laboratory.**

5.4.5 Laboratory Assessments

Page 57; Local Laboratory Samples as follows per the Schedule of Assessments, Table 1: 2nd bullet point
WAS:
• Biochemistry: sodium, potassium, calcium, chloride, glucose, blood urea nitrogen (BUN), creatinine, CPK/CK, total protein, albumin.
IS AMENDED TO:
• Biochemistry: sodium, potassium, calcium, chloride**, phosphorus**, glucose, blood urea nitrogen (BUN), creatinine, CPK/CK, total protein, albumin.

5.4.5 Laboratory Assessments
Page 57; Local Laboratory Samples as follows per the Schedule of Assessments, Table 1: 6th bullet point
ADDED:
• **Urine protein: creatinine ratio**

5.4.5 Laboratory Assessments
Page 58, last bullet point
ADDED:
• **Safety labs (hematology, biochemistry, hepatic profile, urine protein: creatinine ratio and urinalysis) drawn by Home Health Care for Investigator sites utilizing this service will be analyzed by the Central Laboratory.**

5.4.7 Home Health Care Service
Page 58; 2nd bullet point
WAS:
• CMV Plasma Viral Load Testing Visits (Central Laboratory Testing) at Day 100, 128, 142, 170, 198, 230, 290, 320, 350 and 380. (Days 100 and 198 visit windows correspond with Visits 3 and 11.)
IS AMENDED TO:
• CMV Plasma Viral Load Testing Visits (Central Laboratory Testing) at Day 100, **114,** 128, 142, **156,** 170, 198, 230, 290, 320, 350**,** and 380. (Days 100 and 198~~ visit windows~~ **CMV testing must** correspond **appropriately** with **visit windows for** Visits 3 and 11~~.~~**) in order to be combined).**

5.4.8 Long Term Follow-Up
Page 58
ADDED:
During the long-term follow-up period, if an SAE is identified and deemed possibly or probably related to the study medication, an SAE report on the SAE worksheet must

be sent to the sponsor per Section 5.5.6.

5.5.1 Definition of Adverse Events (AEs)
Page 59; 5th bullet point
ADDED:
• **The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.**

5.5.3 Definition of Serious Adverse Events (SAEs)
Page 60; 7th bullet point
ADDED:
• **The transplant surgery that occurs on Day 0 is not considered an AE or an SAE.**

5.5.6 Reporting of Serious Adverse Events (SAEs)
Page 62; 1st paragraph after bullet points
ADDED:
Spontaneously reported possibly or probably related SAEs that occur outside of the study-defined SAE reporting period, i.e., the Long Term Follow-up, should also be sent to the sponsor in accordance with the protocol defined SAE reporting guidelines.

5.7.1 Blood Sample for Future PGx Analysis (Retrospective PGx Analysis)
Page 64-65
WAS:
A PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. After randomization, but prior to the first dose of Study Drug (see schedule of assessments), subjects who consent to participate in the retrospective pharmacogenomics assessment will have a 5 mL sample of whole blood for possible retrospective PGx analysis will be collected using a vacutainer tube containing EDTA. After collection, gently invert the blood sample 8 to 10 times. The blood collection tube may either be stored upright at 4°C for up to 5 days prior to shipment or stored frozen at -20°C or below at the site for extended storage. Samples will be shipped to a Sponsor designated banking CRO.
IS AMENDED TO:
A PGx research **study** may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues. After randomization, but prior to the first dose of Study Drug (see schedule of assessments), subjects who consent to participate in the retrospective pharmacogenomics assessment will have a 5 mL sample of whole blood **collected** for possible retrospective PGx analysis**. This sample** will be collected using a vacutainer tube containing EDTA. After collection, gently invert the blood sample 8 to 10 times. The blood collection tube may either be stored upright at 4°C for up to 5 days prior to shipment or stored frozen at -20°C or below at the

site for extended storage. Samples will be shipped to a Sponsor designated banking CRO.

6.1.1 Study and Treatment Discontinuation

Page 66

WAS:

Treatment Only Discontinuation:

Subjects will be withdrawn from study treatment if any of the following occur, however, they should continue to be followed according to the protocol Schedule of Assessments (Table 1).

- Investigator's decision that further treatment is not in the best interest of the subject.
- Graft failure.
- Pregnancy (female subjects only).
- Local reactogenicity with a grade ≥ 3 based on the criteria defined in Appendix 4 and is confirmed by the investigator and reported as a Drug Related Adverse Event.
- Systemic reactogenicity, for any grade ≥ 3 fever or any grade 4 systemic reaction within one week of vaccination and is confirmed by the investigator and reported as a Drug Related Adverse Event (Appendix 5).

Subjects who discontinue treatment for these or for other reason(s) but did not withdraw consent should remain in the study and continue to be followed according to the visit schedule through the Long-term Follow-up Period. All study procedures should be completed for these subjects, with the exception of the post-dose Day 14 safety laboratory and reactogenicity assessments/visits for those doses that are not given. Subjects not willing to participate in the study procedures should be asked if they would be willing to be followed annually for mortality through the Long-term Follow-up Period.

IS AMENDED TO:

Study and Treatment Discontinuation:

Subjects will be withdrawn from investigational study treatment and all follow- up assessments and will only be followed for mortality through public records if the following occurs:

- **Withdrawal of consent by the subject.**

Treatment Only Discontinuation:

Subjects will be withdrawn from **investigational** study treatment if any of the following occur, however, they should continue to be followed according to the protocol Schedule of Assessments (Table 1**) and Long Term Follow-up Schedule of Assessments, except post-dose Day 14 safety and laboratory and reactogenicity assessments/visits for those doses not given.**

- Investigator's decision that further treatment is not in the best interest of the subject.
- Graft failure.
- Pregnancy (female subjects only).
- Local reactogenicity with a grade ≥ 3 based on the criteria defined in Appendix 4 and is confirmed by **a health care professional** ~~the investigator~~ and reported as a Drug

Related Adverse Event.

- Systemic reactogenicity, for any grade ≥ 3 fever or any grade 4 systemic reaction within one week of vaccination and is confirmed by **a health care professional** ~~**professional the investigator**~~ and reported as a Drug Related Adverse Event (Appendix 5).
- **Anaphylaxis Grade ≥ 3 per NCI ver. 4.03 criteria.**

Subjects who discontinue **investigational** treatment for these or for other reason(s) but **do** ~~did~~ not withdraw consent should remain in the study and continue to be followed according to the visit schedule through the Long-term Follow-up Period. All study procedures should be completed for these subjects, with the exception of the post-dose Day 14 safety laboratory and reactogenicity assessments/visits for those doses that are not given. Subjects not willing to participate in the study procedures should be asked if they would be willing to be followed annually for mortality through the Long-term Follow-up Period.

7 STATISTICAL METHODOLOGY

Page 66

WAS:

A Statistical Analysis Plan (SAP) will be written by the responsible biostatistician of APGD to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest.

IS AMENDED TO:

A Statistical Analysis Plan (SAP) will be written by the responsible biostatistician of APGD to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database ~~soft~~ lock at the latest.

7.4.1.1 Primary Analysis

Page 68; 1st paragraph of section

WAS:

The primary efficacy endpoint, the incidence of CMV viremia (defined as plasma viral load ≥ 250 IU/mL by central assay) through one year post first Study Drug injection, in subjects receiving a kidney from a living or deceased donor**,** will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by use of anti-thymocyte globulin (ATG) as induction therapy and by receipt of a kidney from a living or deceased donor.

IS AMENDED TO:

The primary efficacy endpoint, the incidence of CMV viremia (defined as plasma viral load ≥ **1000**~~250~~ IU/mL by central assay) through one year post first Study Drug injection, in subjects receiving a kidney from a living or deceased donor**,** will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by use of anti-thymocyte globulin (ATG) as induction therapy and by receipt of a kidney from a living or deceased donor.

7.4.3 Analysis of Exploratory Endpoints

Page 69-70

WAS:

The exploratory endpoints in this study include:

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ 250 IU/mL by central assay) through one year post first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of CMV viral load of ≥ 250 IU/mL by central assay through one year post first Study Drug injection.
- Peak CMV viral load through one year first Study Drug injection.
- Total viral load through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Incidence of viral resistance to ganciclovir or valganciclovir through one year post Study Drug injection as determined by a central laboratory assay.
- Incidence of biopsy-proven acute rejection (BPAR) through one year post Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at month 13 calculated using the 4 variable MDRD formula.
- Incidence of clinically treated acute graft rejection rate through one year post Study Drug injection.
- Health economic and outcomes research (HEOR) scores.
- Patient-reported outcomes:
    - EQ-5D (EuroQol-5 dimensions 5 levels) will be used as a preference-based utility measure of patients' quality of life.
    - KTQ (Kidney Transplant Questionnaire) will be used to evaluate transplant-specific patients' quality of life.
    - SF-12v2 (Short Form Health Survey version 2) will be used to evaluate the overall patients' quality of life.
- Healthcare resource utilization:
    - Resource use will be collected including the following: concomitant medications and procedures, hospitalizations, nonscheduled clinic visits, emergency room visits, skilled nursing facility care, hospice care.

Number of episodes of CMV viral load of ≥ 250 IU/mL and number of episodes of adjudicated CMV-associated disease will each be compared between treatments using Poisson regression controlling for follow-up period and stratification factors.

The incidence endpoints will be each analyzed using CMH method described in 7.4.1.1.

The survival endpoints (time to first event) will be each analyzed in a Cox proportional hazards model. The Cox model will include the randomization factors. The common hazard ratio and confidence limits will be estimated. The 1-sided p-values for testing the hypothesis that the hazard ratio is equal to unity will be calculated. The Kaplan-Meier estimates of survival curves for the treatment groups will be displayed.

Peak CMV viral load and total CMV viral load through one year post first Study Drug

injection will be compared using Wilcoxon rank-sum tests.

IS AMENDED TO:

The exploratory endpoints in this study include:

- Number of opportunistic infections other than CMV through one year post first Study Drug injection.
- Time to first CMV viremia (defined as plasma viral load of ≥ **1000**~~250~~ IU/mL by central assay) through one year post first Study Drug injection.
- Time to first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Number of episodes of CMV viral load of ≥ **1000**~~250~~ IU/mL by central assay through one year post first Study Drug injection.
- Peak CMV viral load through one year first Study Drug injection.
- **Viral load area under the curve (AUC), as a measure of "cumulative** ~~Total~~ viral load**"** through one year post first Study Drug injection.
- Number of episodes of adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease, through one year post first Study Drug injection.
- Incidence of viral resistance to ganciclovir or valganciclovir through one year post Study Drug injection as determined by a central laboratory assay.
- Incidence of biopsy-proven **(T or B cell)**~~acute~~ rejection (BPAR)**(Banff 2007 Grade ≥ 1**) through one year post Study Drug injection.
- Estimated glomerular filtration rate (eGFR) at **the last study visit calculated**~~month 13 calculated~~ using the 4 variable MDRD formula.
- Incidence of clinically treated acute graft rejection rate through one year post Study Drug injection.
- Health economic and outcomes research (HEOR) scores.
- Patient-reported outcomes:
    - EQ-5D (EuroQol-5 dimensions 5 levels) will be used as a preference-based utility measure of patients' quality of life.
    - KTQ (Kidney Transplant Questionnaire) will be used to evaluate transplant-specific patients' quality of life.
    - SF-12v2 (Short Form Health Survey version 2) will be used to evaluate the overall patients' quality of life.
- Healthcare resource utilization:
    - Resource use will be collected including the following: **hospitalizations recorded as number of days in the Intensive Care Unit, Step-down Unit, and general medical ward, (including emergency room visits greater than 24 hours);) also non-protocol- related physician visits and emergency room visits less than 24 hours** ~~concomitant medications and procedures, hospitalizations, nonscheduled clinic visits, emergency room visits, skilled nursing facility care, hospice care.~~

Number of episodes of CMV viral load of ≥ **1000**~~250~~ IU/mL and number of episodes of adjudicated CMV-associated disease will each be compared between treatments using Poisson regression controlling for follow-up period and stratification factors. The incidence endpoints will be each analyzed using CMH method described in 7.4.1.1. The survival endpoints (time to first event) will be each analyzed in a Cox proportional hazards model. The Cox model will include the randomization factors. The common hazard ratio and confidence limits will be estimated. The 1-sided p-values for testing the hypothesis that the hazard ratio is equal to unity will be calculated. The Kaplan-Meier estimates of survival curves for the treatment groups will be displayed. Peak CMV viral load and **AUC**~~total CMV viral load~~ through one year post first Study Drug injection will be compared using Wilcoxon rank-sum tests.

7.6.1 Adverse Events
Page 72; 8th paragraph
WAS:
Subgroups analyses for age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), deceased donor criteria (DCD, non-DCD), and the use of anti-thymocyte globulin (ATG) as induction therapy criteria (yes/no) will be performed for the following summaries:
IS AMENDED TO:
Subgroups analyses for age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), ~~deceased donor criteria (DCD, non-DCD),~~ and the use of anti-thymocyte globulin (ATG) ~~as induction therapy criteria~~ (yes/no) will be performed for the following summaries:

7.6.2 Clinical Laboratory Evaluation
Page 73; 5th paragraph
WAS:
Subgroups analyses for age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), deceased donor criteria (DCD, non-DCD), and the use of anti-thymocyte globulin (ATG) as induction therapy criteria (yes/no) will be performed for the following summaries:
IS AMENDED TO:
Subgroups analyses for age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), ~~deceased donor criteria (DCD, non-DCD),~~ and the use of anti-thymocyte globulin (ATG) ~~as induction therapy criteria~~ (yes/no) will be performed for the following summaries:

7.6.3 Vital Signs Evaluation
Page 73; 3rd paragraph
WAS:
The analysis of vital signs described above will also be performed by the following subgroups: age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), deceased donor criteria (DCD, non-DCD), and the use of anti-thymocyte globulin (ATG) as

induction therapy criteria (yes/no).
IS AMENDED TO:
The analysis of vital signs described above will also be performed by the following subgroups: age group (< 65, ≥ 65), race group (white, black, other), sex (male, female), deceased donor ~~criteria (DCD, non-DCD),~~ and the use of anti-thymocyte globulin (ATG) ~~as induction therapy criteria~~ (yes/no).

12.1 Appendix 1: List of Excluded Concomitant Medications
Page 85
WAS:
● Investigational research products through completion of Day 395 visit (Visit 13) ● Alemtuzumab through completion of the Day 395 (Visit 13). ● Rituximab through completion of the Day 395 visit (Visit 13), except for Post-Transplant Lymphoproliferative Disorder. ● Prophylactic use of CMV immunoglobulin. ● Live attenuated vaccines within one month (30 days) prior to each dose of Study Drug. ● Subunit or killed vaccines within 14 days before any Study Drug injection. ● Anticoagulants, within 5 half-lives of Study Drug administration, including but not limited to vitamin K antagonists, heparin or its derivatives, low molecular weight heparin, factor X inhibitors, or thrombin inhibitors. Low dose anticoagulants that are used for prevention of deep vein thrombosis and antiplatelet agents are allowed.
IS AMENDED TO:
● Investigational research products through completion of Day 395 visit (Visit 13) ~~● Alemtuzumab through completion of the Day 395 (Visit 13).~~ ~~● Rituximab through completion of the Day 395 visit (Visit 13), except for Post-Transplant Lymphoproliferative Disorder.~~ ● **Planned Alemtuzumab and, anti-CD20 antibodies (including rituximab), eculizumab or bortezomib are not allowed from Day of Randomization through the Primary Study Period (Day 395). These treatments may be given after the Day of Randomization if clinically indicated.** ● Prophylactic use of CMV immunoglobulin. ● Live attenuated vaccines within one month (30 days) prior to each dose of Study Drug. ● Subunit or killed vaccines within 14 days before any Study Drug injection. ● Anticoagulants, within 5 half-lives of Study Drug administration, including but not limited to vitamin K antagonists, heparin or its derivatives, low molecular weight heparin, factor X inhibitors, or thrombin inhibitors. Low dose anticoagulants that are used for prevention of deep vein thrombosis and antiplatelet agents are allowed.

12.2 Appendix 2: Laboratory Tests
Page 87

ADDED:		
Urine protein: creatinine ratio	**Screening (V1) and Visits 2-11 & 13**	• **Protein: creatinine ratio**

12.5 Appendix 5: Grading of Signs of Systemic Reactogenicity

Page 87

ADDED:

Vital Signs†**				

†Pre- dosing vital signs are to be used as baseline values for determining changes post Study Drug Injection.

12.5 Appendix 5: Grading of Signs of Systemic Reactogenicity

Page 87

WAS:

Bradycardia-beats per minute	Decrease in hear rate 5-10 beats/minute	Decrease in heart rate 11-15 beats/minute	Decrease in heart rate <15 beats/minute	ER visit or hospitalization for arrhythmia

IS AMENDED TO:

Bradycardia-beats per minute	Decrease in heart rate 5-10 beats/minute	Decrease in heart rate 11-15 beats/minute	Decrease in heart rate ≤ > 15 beats/minute	ER visit or hospitalization for arrhythmia

12.7 Appendix 7: Definition of CMV Disease in Solid Organ Transplant Recipients

Page 94

WAS:

Retinitis	Not applicable	Lesions typical of CMV retinitis must be confirmed by an ophthalmologist

IS AMENDED TO:

Retinitis	Not applicable	Lesions typical of CMV retinitis must be confirmed by an ophthalmologist **or by detection of CMV by culture or PCR of vitreous fluid**

12.10 Appendix 10: Liver Safety Monitoring and Assessment

Page98, 1st paragraph

WAS:

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN, or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

IS AMENDED TO:

Any subject enrolled in a clinical study with active drug therapy who reveals an increase of serum aminotransferases (AT) to > 3 × **baseline value and greater than 3X** ULN, or bilirubin > 2 × **baseline value and greater than** 2X ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies **in**~~forin~~ which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. **As local laboratories are utilized for this study, the investigator must report a repeat confirmation of moderate or severe liver abnormalities to the Medical Monitor within 48-72 hours of the test results.** Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

12.10 Appendix 10: Liver Safety Monitoring and Assessment

Page 98, Definition of Liver Abnormalities, 1st paragraph

WAS:

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3× ULN	or	> 2× ULN
Severe*	> 3× ULN	and	> 2× ULN

IS AMENDED TO:

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3× **baseline value & > 3 x** ULN	or	> 2× **baseline value & > 3 x** ULN
Severe*	> 3× **baseline value & > 3 x** ULN	and	> 2× **baseline value & > 3 x** ULN

12.16 Appendix 16: Retrospective Pharmacogenomics (PGx) Sub-Study
Page 110, 1st and 2nd paragraphs
WAS:
PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by one or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug. OBJECTIVES The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues.
IS AMENDED TO:
PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. ~~As many diseases may be influenced by one or more genetic variations,~~ PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug. OBJECTIVES The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, ~~pharmacokinetics,~~ and toxicity/safety issues.

12.16 Appendix 16: Retrospective Pharmacogenomics (PGx) Sub-Study
Page 111, last paragraph
WAS:
Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.
IS AMENDED TO:
~~Exploratory~~**Retrospective** PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information

that is obtained from the PGx analysis will be the property of Astellas.

12.17 Appendix 17: Long-term Follow-up Questionnaire
Page112, 1st paragraph
WAS:
Subjects will be contacted by telephone annually for 5.5 years starting at 1.5 years after the first injection of Study Drug to evaluate for long-term safety related to the DNA vaccine. Items to be assessed by questionnaire and available medical records include mortality, development of any new cancer, development of infection requiring hospitalization, graft survival, creatinine and local immune-mediated reactions.
IS AMENDED TO:
Subjects will be contacted by telephone annually for ~~5.5~~**4** years starting at 1.5 years after the first injection of Study Drug to evaluate for long-term safety related to the DNA vaccine. Items to be assessed by questionnaire and available medical records include mortality, development of any new cancer, development of infection requiring hospitalization, graft survival, creatinine and local immune-mediated reactions. **During the long-term follow-up period, if an SAE is identified and deemed possibly or probably related to the study medication, an SAE report on the SAE worksheet must be sent to the sponsor per Section 5.5.6.**

12.18 Appendix 18: Health Economic Assessment (Inpatient and Outpatient Utilization)
Page113-114
WAS:
Are there any Inpatient Care visits to report? □Yes □No If Yes, Date of Admission (dd/MMM/yyyy) Admission Unit/Floor (Choose one only) □ ICU □ Hospital Ward □ Nursing Home/Long Term Care Facility □ Skilled Nursing Facility □ Rehabilitation Center □ Private Residence with Home Health Care □ Home with Hospice □ Home without any Services □ Other: _____(Please specify)

Primary Reason (Diagnosis) for Admission or Transfer:_____

ICD-9 (for US sites only):

Date of Discharge dd/MMM/yyyy

Discharge Unit/Floor (Choose one only)

□ ICU

□ Hospital Ward

□ Nursing Home/Long Term Care Facility

□ Skilled Nursing Facility

□ Rehabilitation Center

□ Private Residence with Home Health Care

□ Home with Hospice

□ Home without any Services

□ Other: _____(Please specify)

Are there any Outpatient Care visits to report? □Yes □No

If Yes, Date of Visit (dd/MMM/yyyy)

Place of Service (Choose one only)

□ Emergency Room visits (without admittance)

□ Physician Visits

□ Outpatient Lab/Radiology visits

□ Outpatient (Physical/Speech, etc.) Therapy Center

□ Other: _____(Please specify)

IS AMENDED TO:

Are there any Inpatient Care visits to report? □Yes □No

If Yes, ~~Date~~**please record the number** of **days the patient was admitted to:** ~~Admission (dd/MMM/yyyy)~~

Admission Unit/Floor ~~(Choose one only)~~

~~□~~ ICU **Days**_____

~~□~~ **# of Days**

Step-down Unit Days_____

# of Days

Hospital **General Medical/Surgical** Ward **Days**_____

# of Days

~~☐ Nursing Home/Long Term Care Facility~~

~~☐ Skilled Nursing Facility~~

~~☐ Rehabilitation Center~~

~~☐ Private Residence with Home Health Care~~

~~☐ Home with Hospice~~

~~☐ Home without any Services~~

~~☐ Other: _____(Please specify)~~

Was there an Emergency Room visit greater than 24 hours (without admittance)?
☐Yes ☐No

If yes, please indicate the number of Emergency Room days_____
# of days

Primary Reason (Diagnosis) for Admission**:**_____ ~~or Transfer:_____~~

If a US site, please insert the ICD-9 ~~(~~**code** for **the diagnosis.** ~~US sites only):~~

~~Date of Discharge dd/MMM/yyyy~~

~~Discharge Unit/Floor (Choose one only)~~

~~☐ ICU~~

~~☐ Hospital Ward~~

~~☐ Nursing Home/Long Term Care Facility~~

~~☐ Skilled Nursing Facility~~

~~☐ Rehabilitation Center~~

~~☐ Private Residence with Home Health Care~~

~~☐ Home with Hospice~~

~~☐ Home without any Services~~

~~☐ Other: _____(Please specify)~~

If more than one Inpatient Care visit to report, please record diagnosis/ICD-9 code for each admission, and the number of days as noted above.

Are there any ~~Outpatient Care~~ **Non- Protocol- related Physician** visits to report? □Yes □No

If Yes **please indicate the number of Visits:** ~~Date of Visit (dd/MMM/yyyy)~~

~~Place of Service (Choose one only)~~

~~□ Emergency Room (without admittance)~~

~~□~~ Physician Visits_____

# of visits

~~□ Outpatient Lab/Radiology visits~~

~~□ Outpatient (Physical/Speech, etc.) Therapy Center~~

~~□ Other: _____(Please specify)~~

14 SPONSOR'S SIGNATURES

1. SPONSOR'S SIGNATURES

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial to Evaluate the Efficacy and Safety of a Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seronegative Kidney Transplant Recipients Receiving an Organ from a CMV-Seropositive Donor

ISN/Protocol 0113-CL-2001 / Version 3.0

Incorporating Substantial Amendment 2, 06 January 2014