STATISTICAL ANALYSIS PLAN

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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

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AC	Adjudication Committee
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
APGD	Astellas Pharma Global Development
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
ATG	Anti-thymocyte globulin
AUC	Area under the concentration-time curve
AVT	Antiviral therapy
BMI	Body Mass Index
BPAR	Biopsy proven acute rejection
BPP	Bayesian predictive probability
CI	Confidence Intervals
CMH	Cochran–Mantel–Haenszel test
CMV	Cytomegalovirus
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
D+R-	Donor CMV seropositive and recipient CMV seronegative
EBV	Epstein Barr virus
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
HEA	Health Economic Assessment
ICH	International Conference on Harmonization
KTQ	Kidney transplant questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease Study
NCI	National Cancer Institute
PCR	Polymerase chain reaction
PGx	Pharmacogenomics
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SF-12	Short Form health survey 12 item
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

List of Key Terms

Terms	Definition of terms
Endpoint	A variable that pertains to the trial objectives
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.
Adverse Event	An adverse event is any untoward medical occurrence in a subject administered a study drug or undergone a study procedure which does not necessarily have a causal relationship with the treatment.
Adjudication Committee	A group of clinical experts who will create specific, standardised event definitions for each suspected events of interest including all cases of CMV syndrome, CMV tissue-invasive disease and CMV-specific antiviral therapy.
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 measurements / evaluation prior to the first dose of randomized therapy is considered the baseline measure/evaluation.
CMV Viremia	Presence of CMV in the blood.
Double-Blind	Neither the subjects of the trial nor the persons administering the trial know the true treatments.
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.
Hard Lock	Hard lock of a study database occurs after all issues discovered in final data review have been resolved and it is expected that no more changes to the study database will occur. Only after hard lock are treatment assignments unblinded.
Independent Statistician	The statistician who is not part of the study team
Investigational Period	The time between the first dose of study drug (Visit 2) through one year post first dose of study drug (Visit 13).
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 Study Period	From first study drug injection (Day 1) to the time of early termination or 1-year post first study drug injection (Day 380), whichever is first.
Primary Study Withdrawal	A subject who is randomized but does not complete the Primary Study Period for any reason.
Protocol-defined CMV viremia	CMV plasma viral load $\geq$1000 IU/mL as assessed by the central laboratory.

Terms	Definition of terms
Prophylactic Therapy	A treatment administered prior to the detectable presence of infection or disease as a preventative measure.
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 at +30 post transplant .
Screening	The process for identifying a candidate for the study and evaluating their eligibility to participate. This occurs between days -14 prior to Transplant and +30 days post Transplant.
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.
Soft Lock	Soft lock of a study database occurs when all data have been entered and queried and the database is considered ready for final data review. Treatment assignments remain blinded during soft lock and the final data review.
Subject	An individual who participates in a clinical trial.
Treatment Emergent Adverse Events	Adverse events occurring after the first dose of study drug and through one year post first dose of study drug.
Treatment Period	The period of time from the first dose of study drug through the last dose of study drug.

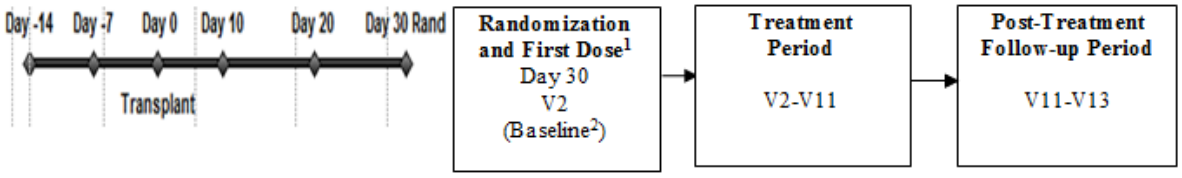
1 INTRODUCTION

The SAP is finalized and signed prior to database hard lock and unblinding of treatment groups.

The changes to the original SAP that affect the analyses are summarized in Appendix 4. Any changes from the planned analyses in the final SAP will be explained in the Clinical Study Report (CSR).

2 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.
3. The date of transplant (day of skin closure) defines Day 0 and all visit days are relative to Day 0.
4. 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.
5. Informed consent must be obtained prior to the performance of any study-related procedure.
6. Subjects will be assigned a subject number for use throughout the study at the Screening Visit via the Interactive Response Technology (IRT) system.

Footnotes continue on next page

7. 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.
8. Medical history must include demographics, (age, gender, race), diagnosis for renal failure, length of time on dialysis, history of prior kidney transplant, and diabetes.
9. 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.
10. 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.
11. 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 [redacted] for Investigator sites utilizing this service will be analyzed by the Central Laboratory.
12. 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.
13. 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.
14. 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.
15. Transplant information includes type of transplant (Living Related Donor, Living Unrelated Donor, or Deceased Donor).

Footnotes continue on next page

16. 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]).
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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).
23. 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.
24. 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.
25. Specimen drawn and sent to the Central Laboratory.
26. 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.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

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.

3.2 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 about 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.

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.

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.

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.

3.3 Randomization

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.

Subjects who subsequently meet the inclusion/exclusion criteria will be randomly assigned to receive either ASP0113 or placebo. The randomization to treatment will be equally allocated (i.e., 1:1) and 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 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 and designated staff administering the Study Drug.

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).

4 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 ≥ 1000 IU/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 Chi-square test with a type 1 error rate of 5%. To allow for drop-out (randomized but not evaluable), 70 subjects per arm will be enrolled for a total sample size of 140 subjects.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

This SAP includes the data analysis for the primary study period which is defined as 1-year post first study drug injection. Certain data summary will consider analysis windows as specified in relevant sections. The long-term follow-up period is not covered by this SAP.

5.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all randomized subjects who received at least one dose of randomized study drug and who have at least one post dose viral load assessment within 1-year post first injection by central laboratory.

Specifically, the following will lead to a subject's exclusion from the FAS:

- Did not take study drug , or
- Had no viral load assessment by central laboratory after first study drug injection

The FAS will be the primary analysis set for efficacy analyses and for summaries of selected demographic and baseline characteristics. For this population, data will be analyzed by the treatment group that patients were randomized to.

5.2 Safety Analysis Set (SAF)

The Safety Analysis Set consists of all randomized subjects who received at least one dose of study drug. For the SAF, data will be analyzed according to the study medication that subjects received as the first dose even if it differs from what they were randomized to.

5.3 Immunogenicity Analysis Set (IAS)

The Immunogenicity Analysis Set (IAS) will include subjects who received randomized study drug and for whom at least one post-transplant immunogenicity measurement is available.

The IAS will be used for analyses of the immunogenicity data.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

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

6.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are: :

- Proportion of subjects with Adjudicated CMV-associated disease including CMV syndrome and CMV tissue-invasive disease.
- Proportion of subjects with plasma viral load ≥ the lower limit of quantification [LLOQ] assessed by central laboratory.
- Proportion of subjects who took Adjudicated CMV-specific antiviral therapy for the treatment of CMV viremia or disease.
- Proportion of subjects with graft survival.

6.1.3 Exploratory Efficacy Endpoints

- Number of patients with at least one opportunistic infections other than CMV
- 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) adjusted for duration 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.

- Proportion of subjects with viral resistance to ganciclovir or valganciclovir through one year post first Study Drug injection as determined by central laboratory assay.
- Proportion of subjects with biopsy-proven (T or B cell) acute rejection (BPAR) (Banff 2007 Grade $\geq$ 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.
- Proportion of subjects with clinically treated acute graft rejection through one year post first Study Drug injection.

6.1.4 Immunogenicity Variables

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 cultured ELISpot .
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:

Dose 1, Post Dose 2, Dose 3, Post Dose 4, Dose 5, and End of Study Visit:

- 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.

6.1.5 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 one year post first study drug injection.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events
- Clinical laboratory variables
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and weight)
- Physical examination.

6.3 Pharmacokinetic Variables

Not applicable.

6.4 Pharmacodynamic Variables

Not applicable.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

All statistical analyses and summary information will be generated according to this analysis plan and any deviations from this plan will be documented in the clinical study report. Any numerical rounding should be performed at the end of calculations. The p-values will be displayed with 3 decimal places. Statistical significance will be determined prior to rounding the p-value.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing datathus the percentages will add up to 100%. Baseline will be the last non-missing value on or prior to first stidy drug unless otherwise specified.

All efficacy comparisons will be tested at the 1-sided 0.05 significance level. Confidence intervals for efficacy estimates, if provided, will be constructed at 2-sided 90% level.

All data processing, summarization, and analyses will be performed using SAS® Version 9.1.3 or higher on Unix.

This SAP includes the data analysis for the primary study period (ie, 1-year post first study drug injection) which is defined as data collected through day 380 (=365+14+1 day). Certain data summary will consider analysis window as specified in each section. The long-term follow-up period is not covered by this SAP and will be managed in a separate SAP.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects with informed consent, discontinued before randomization, and randomized;
- Number and percentage of subjects randomized in each analysis set, by treatment group;
- Number and percentage of subjects completed and discontinued treatment, by reason for treatment discontinuation for randomized subjects, by treatment group;
- Number and percentage of subjects completed and discontinued the study, by reasons for study discontinuation for randomized subjects and by treatment group;

7.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all randomized subjects. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment group and total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. 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.

7.2.3 Demographic and Medical History

Demographic and other baseline characteristics will be summarized by descriptive statistics for FAS and SAF populations.

Number and percentage of subjects randomized in each country and site will be presented by treatment group for the SAF.

Descriptive statistics for age, weight, body mass index (BMI), BMI categories (<25, 25 to <30, and ≥30 kg/m^2), height at study entry, and the demographic categories defined below will be presented.

Demographics	**Categories**
Ethnicity	Not Hispanic or Latino
	Hispanic or Latino
Race	White
	Black
	Other
Age group	< 65 years
	≥65 years
Gender	Female
	Male

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group for the SAF.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the SAF.

A drug stopped before or on the day of the first study drug injection will be defined as previous medication. And a drug started within the primary stusy period will be defined as concomitant medication. As with previous medication, concomitant medication will be summarized for each treatment group by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

7.2.5 Antiviral therapies

Antiviral therapies, including those used for reasons other than CMV infection will be summarized by reason for use.

All subjects should receive 100 days of prophylactic valganciclovir or ganciclovir continuously starting within 10 days of transplant. The numbers of days on the prophylaxis will be summarized by treatment for the SAF.

7.2.6 Transplant Information

The following characteristics of the transplant procedure will be summarized by treatment for the SAF.

- Use of anti-thymocyte globulin (ATG) (Yes/No)
- Type of transplant (living donor & ATG=Yes/ living donor & ATG=No/ deceased donor & ATG=Yes/ deceased donor & ATG=No)
- Recipient and donor relatedness (living related donor, living unrelated donor, deceased donor)

- Donor demographics (age, gender, race)
- Recipient and donor HLA typing
- HLA cross match at time of transplant (see Appendix 1 for how the cross match is determined)
- Recipient and donor ABO types
- Recipient and donor Hepatitis B virus, Hepatitis C virus, and Epstein-Barr Virus serostatus, if available, and HCV PCR RNA, (if available)
- Organ preservation method

7.3 Study Drug

Descriptive statistics for total number of injections subject received and the time from first dose to final dose of study drug will be presented by treatment. Furthermore, the number and percentage of subjects receiving study drug injection at each scheduled dose will be presented by treatment. These summaries will be produced for the SAF.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with CMV viremia which is defined as plasma viral load ≥ 1000 IU/mL assessed by central assay through one year post first Study Drug injection. CMV viral load tests are scheduled once every 2 weeks for the first 8 tests starting 100 days from transplant and subsequently once per month for 7 more tests. In addition, a subject may have unscheduled tests (suspect CMV syndrome or CMV tissue-invasive disease) by the local laboratory so that the subject can be treated promptly with antiviral therapy (AVT) if needed. Everytime a local laboratory is performed, the sample should also be sent to the central laboratory for assessment. The CMV viral load collected from the central laboratory after first injection (Day 1) through day 380 (=365+14+1) that were collected as scheduled or unscheduled assessments will be utilized.

A patient who discontinue the study without a positive CMV viral load will be imputed as having a CMV viremia. A patient who has more than one time with viral load ≥ 1000 IU/mL by central assay will be counted once in this summary. Any unscheduled central laboratory values within the window will be included.

A Cochran-Mantel-Haenszel (CMH) test at the 1-sided 5% level stratified by use of anti-thymocyte globulin (ATG) and by receipt of a kidney from a living or deceased donor will be used to analyze the primary endpoint of CMV incidence rate.

The null and alternative hypotheses for this comparison are:

H0: Common Odds Ratio = 1.

H1: Common Odds Ratio < 1.

The odds ratio is defined as the ratio of odds of viremia in the ASP0113 group to that in the placebo group. The 1-sided p-value with the 2-sided exact 90% confidence interval for the

common odds ratio will be calculated (in SAS specifying the comor option in the exact statement of proc freq).

The primary analysis will be conducted for the FAS population.

7.4.1.2 Sensitivity Analysis for Primary Efficacy Endpoint

Three sensitivity analyses for the primary efficacy endpoint will be conducted.

An analysis identical to the primary analysis described in Section 7.4.1.1 will be repeated:

- A subject with two consecutive missing central laboratory CMV assessments
- Composite endpoint of either CMV viral load >=1000 IU/mL by central labortorys OR use of AVT per adjudication

The third sensitivity analysis will be conducted using the Kaplan-Meier method for the FAS population. Time to first occurrence of a patient's CMV viremia will be included and treatment groups will be compared using a log-rank test.

Time to first event (in days) is calculated for each subject by taking the difference between the date of first study drug injection and the date of first event during the primary study period plus 1. If a subject does not have the event of interest through Day 380 the subject will be censored at Day 380. If a subject discontinues the study (or lost to follow up) before Day 380 then the subject will be considered as censored at last assessment. If the event occurs outside the primary study period it will not be counted for the analysis.

7.4.1.3 Subgroup Analysis of Primary Efficacy Endpoint

Subgroup analysis on the primary efficacy endpoint will be performed with a logistic model including treatment, subgroup, and treatment by subgroup interaction as explanatory variables. A subgroup with a level that has fewer than 10 patients within any treatment group, the level will be excluded from the interaction test while descriptive statistics will be provided. If none or only one level of the subgroup meets the 10-subject criterion no subgroup analysis will be performed. The proportion, odds ratio per subgroup factor and its 2-sided 90% confidence intervals will be calculated. As this is a phase 2 study and the interaction test between the treatment group and the subgroup factors should be interpreted with a caution, the p-value from the interaction test will be compared to 0.15.

The subgroup analysis will be performed for the FAS according to:

- levels of randomization strata
- use of ATG, alemtuzumab, or rituximab after randomization
- use of ATG after randomization
- use of alemtuzumab after randomization
- use of rituximab after randomization
- use of alemtuzumab or ATG after randomization
- kidney preservation method (cold, PUMP)
- age group (<65, ≥65)
- race (white, balck, other)

- gender (male, female).

7.4.2 Analysis of Secondary Efficacy Endpoints

The secondary endpoints defined below are binary with yes/no coutcomes. These secondary endpoints will be analyzed on FAS using the same method for the primary efficacy endpoint analysis described in Section 7.4.1.1

7.4.2.1 Adjudicated Endpoints

An independent panel of medical experts will adjudicate the events below through one year post first study drug injection based on blinded data:

- CMV associated disease including CMV syndrome and tissue invasive disease,
- CMV specific antiviral therapy for the treatment of CMV viremia or disease

The proportion of subjects with any of the two adjudicated events will be analyzed separately

7.4.2.2 CMV Viremia Defined as Plasma Viral Load ≥ the Lower Limit of Quantification [LLOQ]) by Central Assay

The central laboroatory will have the LLOQ for CMV viral load assessment. When the viral load is below the LLOQ the actual viral load reading is not possible and will be denoted as ≤LLOQ. If a sunject has any CMV viral load assessment greater than the LLOQ by central laboratory the subject will be classified as viremic. The proportion of subjects with viremia will be analysed. For the purpose of this analysis, the same imputation method should be used as for the primary analysis.

7.4.2.3 Graft Survival

Calculation of graft survival: any subject that does not fit the definition of graft loss as follows during the primary study period will be defined as “yes”: subject death, re-transplant, nephrectomy, or return to permanent dialysis (i.e., for >30 days). The proportion of subjects with graft survival will be analyzed.

7.4.3 Analysis of Exploratory Endpoints

The analyses of all exploratory variables defined in Section 6.1.3 will be performed on the FAS. Each of these variables will be summarized by treatment. If the endpoint is measured at different visits, the variable will be summarized by treatment at each visit and at Final Visit unless stated specifically otherwise.

Comparisons between treatment groups for the following binary variables will be tested using the exact CMH method as described in Section 7.4.1.1

- viral resistance to ganciclovir or valganciclovir
- biopsy-proven acute rejection (BPAR)
- clinically treated acute graft rejection

Viral resistance to ganciclovir or valganciclovir is confirmed by central laboratory. Biopsy proven acute rejection (BPAR) is captured in the CRFs. For acute antibody mediated

rejection with Banff grade ≥ 1 or for T-cell mediated rejection with grade ≥ 1a BPAR will be "yes". Clinicall treated acute graft rejection will be from the CRF.

The time to the first adjudicated CMV disease, including CMV syndrome and CMV tissue-invasive disease will be analized using the the same method as described in the third sensitivity analysis in Section 7.4.1.2

The following count variables may be affected by duration of follow-up which is the time of last assessment from first injection plus 1. Therefore, each of the variable will be compared between treatments using Poisson regression with treatment and randomization stratum as factors offset by follow-up time. The risk ratio, 1-sided 5% p value and the 90% confidence interval for the risk ratio will be presented.

- Number of opportunistic infections other than CMV
- Number of episodes of CMV viral load of ≥ 1000 IU/mL by central assay
- Number of episodes of adjudicated CMV-associated disease, including CMV syndrome and CMV tissue-invasive disease

Classifications of opportunistic infections other than CMV: Any TEAE with the following classifications will be considered and decided by the medical and safety officers of the study team before unblinding case by case if it is an opportunistic infection: (1) SOC: Renal and Urinary disorders and HLGT= Viral infectious disorders, Chlamydial Infections disorder, Mycobacterial infectious disorders, Fungal infectious disorders, Bacterial infectious disorders, Protozoal infectious disorders; (2) SOC: Renal and Urinary disorders and HLT= Genitourinary tract inflammation and infection NEC, Bladder infections and inflammations, Renal infections and inflammation, Urethral infections and inflammations.

Count episodes of the protocol defined CMV viremia:

An episode starts with CMV viral load ≥ 1000 IU/mL by central assay and ends with two consecutive CMV viral load < 1000 IU/mL by central assay separated by at least one week in time. An episode will not be counted if it starts outside the primary study Period.

The ordinal variables below assessed by the central laboratory will be compared between treatments using the stratum-adjusted Wilcoxon rank-sum test. This test is implemented in SAS Proc Freq using the CMH2 option for tests based on row mean scores and SCORES=MODRIDIT option for use of modified standardized rank score within strata:

- Peak CMV viral load
- Cumulative viral load

Calculation of cumulative viral load:

Using the linear trapezoidal rule to calculate the area under the viral load over time curve (AUC) divided by the length of time for each subject.

The eGFR and its change from baseline will be summarized by treatment at each visit and at final visit. The change from baseline to final visit will be compared using analysis of

covariance (ANCOVA) with treatment and randomization stratum as factors and baseline value as a covariate.

Calculation of eGFR:

$$186 \times serum\ creatinine^{-1.154} \times age^{-0.203} \times [1.212\ if\ Black] \times [0.742\ if\ Female]\ ,$$

where serum creatinine is in mg/dL and age in years. The value in either bracket is 1 if the stated condition is not met. If serum creatinine is in SI units (mmol/L) instead of the US units (mg/dL) then its value needs to be converted to the US units first by multiplying a factor of 1/88.4.

Data from KTQ and SF-12 will be listed without any analysis.

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 5 response levels with higher score indicating worse outcome. In addition, it has a visual analogue scale that elicits a self-rating by the respondent of his/her health on a vertical, visual analogue scale where the endpoints are labeled 'The best health you can imagine' (=100) and 'The worst health you can imagine' (=0). (see Appendix 13 of the Protocol).

The EQ-5D score for each domain, the visual analog score and the corresponding changes from baseline will be summarized by treatment at each visit and at final visit.

7.4.4 Analysis of Immunogenicity Variables

T-cell responses to pp65 and gB-specific antibody levels will be summarized by visit and treatment group on the original scale. A plot of each of the immune responses over time by treatment will be produced. The comparisons between treatments will be made at each measurement visit using Wilcoxon rank sum test without adjusting for the multiplicity on the original scale. In addition, each of the immune response variables post baseline on the 10 based log scale will be analyzed using repeated measures model, where the randomization stratum, treatment, time, and treatment by time interaction will be the explainatory variables. The self-consistent sandwich correlation structure will be used. If the test for the time by treatment interaction is significant (p value<0.1) the overall treatment group comparison will not be displayed in the plots.

As an exploratory analysis, the relationship between immunogenicity variables and treatment outcome will be assessed using logistic regression method. The treatment outcome is if subject is free of CMV viremia through one year post-transplant. The optimal cutoff values of the respective immunogenicity variables that will define the treatment outcome will be explored in terms of maximizing the area under the receiver operating characteristic (ROC) curves.

All analyses of immunogenicity variables will be based on the IAS.

7.5 Analysis of Safety

All analysis of safety will be presented by treatment group for the SAF.

7.5.1 Treatment Emergent Adverse Events

The coding dictionary for this study will be MedDRA Version 16.

TEAE is defined as an adverse event observed after the first study drug injection (Day 1) through Day 380. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent. If a subject experiences an event before the first study drug injection and continues during the primary study period, the event will be considered as TEAE only if it has worsened in severity during the primary study period (i.e., it is reported with a new start date).

An overview summary table will include the following:

- Number and percentage of subjects with TEAEs,
- Number and percentage of subjects with drug related TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug injection, and
- Number and percentage of subjects with drug related TEAEs leading to permanent discontinuation of study drug injection, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group. Summaries will be provided for:

- TEAEs
- drug related TEAEs,
- serious TEAEs,
- drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5.0% in any treatment group, and
- common TEAEs that equal to or exceed a threshold of 5.0% in any treatment group.

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. AEs will be graded using National Cancer Institute (NCI)-Commom Terminology Criteria for Adverse

Event (CTCAE) guidelines version 4.03. There are five grades: 1=mild, 2=moderate, 3=severe, 4=life threatening, 5=death. Missing severity will not be imputed.

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized for each treatment group.

TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by severity and by relationship to study drug. If an adverse event changes in severity or relationship, then the subject will be counted only once with the worst severity and highest degree of relationship. Drug related TEAEs will be presented in a similar way by severity.

7.5.2 Adverse Events of Special Interest

The number and percentage of subjects with each protocol defined grade will be summarized by treatment group for each injection visit and for worst grades across visits unless specified otherwise. There should be no imputations for missing values.

7.5.2.1 Acute Local Reactions Assessed by Investigator and Subject

The symptoms of local vaccine reactions and severity grading are defined below:

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

Local reactions assessed by subjects:

Each subject will take 7 day diaries post each injection to recod the symptoms and the corresponding grades as shown above. For each symptom the maximum grade of the 7 day diary associated with each injection visit will be defined as the symptom grade for that visit.

Local reactions assessed by investigators:

Symptoms are assessed one hour post each injection by investigators and the results are captured in the CRFs.

7.5.2.2 Acute Systemic Reactions Assessed by Subjects

The symptoms and grading of systemic vaccine reactions assessed by subjects are defined below:

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
Fever (°C)***	38.0-38.4	38.5-38.9	39.0-40	> 40
(°F)***	100.4-101.1	101.2-102.0	102.1-104	> 104

Each subject will take 7 day diaries post each injection to recod the grades associated with fatigue and myalgia and record the tempertures based on which the protocol defined grade will be derived according the above table. For each symptom the maximum grade of the 7 day diary associated with each injection visit will be defined as the symptom grade for that visit.

7.5.2.3 Acute Systemic Reactions Assessed by Investigators

The symptoms and grading of systemic vaccine reactions assessed by investigators are defined below.

Vital signs are assessed pre- and 1 hour post- each injection. Changes will be used to determine the grades 1-3 according to the charter below. Grade 4 (except for fever related) comes from the SAEs. If any SAE that is considered related to systemic reactions post each injection by the investigators (captured in the CRF) and meets one of the two criteria below will be a grade 4 systemic reaction: (1) PT=Endotracheal Intubation, or (2) PT= Tachycardia, Bradycardia, Hypertension, or Hypotension with NCI- CTCAE v4.03 severity grade ≥4.

Systemic (General)*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life –Threatening (Grade 4)**
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

7.5.2.4 Late Vaccine Reactions

All TEAEs will be reviewed by the Sponsor medical before databased hard lock to determed the terms for late vaccine reactions.

The number and percentage of subjects with each NCI- CTCAE v4.03 severity grade will be presented by treatment group.

7.5.3 Clinical Laboratory Evaluation

The baseline value for clinical laboratory evaluations is the last measurement taken prior to or on the day of the first injection of study drug.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, urine protein, urine creatinine and calculated ratio of protein/creatinine will be summarized descriptively (n, mean, standard deviation, minimum, median, and maximum) by visit. Clinical laboratory samples are drawn at screening, before each study drug injection, at each follow-up point for the injections, and at the last study visit (See Analysis visit window in Section 7.9.3).

Additionally, a within subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized descriptely.

7.5.3.1 Liver function Tests

Patients' liver safety evaluations will be summarized by the following categories:

- ALT **or** AST > 3xULN, > 5xULN, > 10xULN, >20xULN
- ALT > 3xULN, > 5xULN, > 10xULN, >20xULN
- AST > 3xULN, > 5xULN, > 10xULN, >20xULN

- ALP > 1.5xULN, >3xULN
- Total Bilirubin >2xULN
- ALT **or** AST > 3xULN **and** Total Bilirubin > 1.5xULN
- ALT **or** AST > 3xULN **and** Total Bilirubin > 2xULN
- ALT **or** AST > 3xULN **and** ALP< 2xULN **and** Total Bilirubin > 2xULN

The post-baseline values that are collected through day 380 and meeting the above criteria will be included without regards to the baseline values.

7.5.4 Vital Signs

The baseline value for vital signs is the last measurement taken on or prior to the first injection of study drug.

Vital signs (temperature, systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate,) and the change from baseline will be summarized using mean, standard deviation, minimum, median, and maximum by analysis visit (see Section 7.9.3).

7.5.5 Pregnancies

Data will be listed.

7.5.6 Physical Examination

Data will be listed.

7.6 Analysis of PK

Not applicable.

7.7 Analysis of PD

Not applicable.

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

No interim analysis evaluating the efficacy results are planned. The safety data will be monitored by the DMC according to the DMC Charter. Futility analyses with first 50 subjects and with 90 subjects were conducted (Appendix 2). The details will be described in the clinical study report.

At each futility analysis, Bayesian predictive probability of success (*BPP*) that the overall results of the trial will achieve the desired outcome, i.e., viremia rate on ASP0113 is at least 25% less than that on placebo, will be calculated based on the accrued data. If BPP $\leq$ 0.20, then we conclude ASP0113 meets futility criterion.

The 20% cut-off for BPP is determined by simulation studies. The simulation studies cover the following scenarios: for each placebo viremia rate of 0.40, 0.46, and 0.51 the reduction in viremia due to ASP0113 run from 0% (no effect), 10% (marginal reduction), 25% (meaningful reduction), and 45% (significant reduction). Under each scenario, BPP is calculated at each interim look. The 20% cutoff produces satisfactory overall operating

characteristics of stopping the study early when there is little effect and preserving the power when ASP0113 shows the hypothized effect.

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.

Production of tables and listings will be performed by the independent statistician at Astellas / independent Data Analysis programmer at [redacted] No member of the clinical trial team will have access to the reporting data base or will review the final tables and listings created for the DMC.

The primary responsibility of the DMC will be to monitor the trial for safety and futility concerns. The DMC will not stop the trial based on efficacy advantages. Therefore, the significance level need not be adjusted for the interim looks.

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

7.9.1 Missing Data

In the analysis of the primary endpoint, subjects who are lost to follow-up will be imputed as having viremia. Otherwise, viremia will not be imputed. Only observed viral loads from central labs meeting the definition of viremia will be counted.

Time to event variables will be considered censored at the time of the last assessment. Time to the first protocol-defined CMV viremia will be considered censored at the time of the last recorded central laboratory CMV measurement.

The start and stop dates of AEs and concomitant medication will be imputed to allocate the concomitant medication and AEs to a treatment group, in addition to determining 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.

In case of missing partial start and stop dates for concomitant medications, the following rules will be used:

If start date is missing or partial:

- if month is missing, use January
- if day is missing, use the first day of the month under consideration
- if year is missing, use year of the informed consent date
- if entire date is missing, use informed consent date

If stop date is missing or partial:

- if month is missing, use December
- if day is missing, use the last day of the month under consideration
- if year or the entire date is missing, set to December 31st, 2099

If the imputed start date is after the stop date, then the imputed start date will be one day prior to the stop date.

For AEs, a missing or incomplete onset date will be imputed according to the following conventions for the purpose of defining TEAE.

1) Missing year, the AE will be count as TEAE
2) Missing month, the AE will be counted as TEAE if the year is equal to the consent year or one year later.
3) Missing date, using the last date of the month to determine TEAE.

No imputation of missing data for other variables will be done.

7.9.2 Outliers

All values will be included in the analyses.

7.9.3 Visit Windows

The screening visit, all dosing visits, post dosing visits, Month 8 and End of Study visits for analyses will be based on dates relative to date of first study drug injection (Day 1) according to the table below:

CRF Visit	Target day	Range	Analysis visit
1	-43 to 1	-43 to 1	Screening
2	1	1 to 1	Dose 1
3	15	12-18	Post Dose 1
4	31	26-36	Dose 2
5	45	42-48	Post Dose 2
6	61	56-66	Dose 3
7	75	72-78	Post Dose 3
8	91	86-96	Dose 4
9	105	102-108	Post Dose 4
10	151	146-156	Dose 5
11	165	162-168	Post Dose 5
12	241	231-251	Month 8
13	366	352-380	End of Study

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 14 days after dose 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.

If there is ambiguity about numbering of a visit, then visit number will be assigned so that no two visits are assigned the same visit number, and (1) the value which assessment day is the closest to the defined target day within these windows is used; (2) if two values are equally close, the later is used in the analysis; (3) if the assessment should be performed before each dosing then the value collected last before dosing will be used; (4) if the assessment should be performed on the same day as a dosing day then the assessments closest to the day of the injection should be used.

Analyses will not exclude subject data due to the subject's failure to comply with the visit schedule.

8 REFERENCES

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9 APPENDICES

9.1 Appendix 1: Handling of the Human Leukocyte Antigen (HLA) Mismatching

For the comparison of the HLA types between the donor and the recipient, the following steps should be done to calculate the number of HLA mismatches:

1. If the entry for a locus is a numeric code and a dash (or missing), then the dash for that locus is to be replaced (for calculation only) by the numeric code (homozygote).
2. The following rules should be applied when calculating the number of mismatches within a HLA A, B, and DR locus:
   - If both codes are missing in either the donor or recipient, the number of mismatches is unknown (missing)
   - If the two codes are non-missing and identical for the recipient and the donor (without regard to the order) or the donor is homozygote and the donor code matches either one of the recipient's codes then the number of mismatches is 0.

Examples:

Donor	Recipient	Mismatch
A1 A2	A2 A1	0
A2 A2	A2 A1	0

   - If one code from the donor exists in the recipient but the other code is different between the donor and recipient or the donor has identical codes (homozygote) but they don't match either code in the recipient, then the number of mismatches is 1.

Examples:

Donor	Recipient	Mismatch
A2 A3	A2 A1	1
A2 A3	A2 A2	1
A2 A2	A3 A4	1
A2 A2	A1 A1	1

   - If the donor is not homozygote and all codes are different between the donor and the recipient then the number of mismatches is 2.

Example:

Donor	Recipient	Mismatch
A1 A2	A3 A4	2

3. If the number of mismatches from any of the three loci are missing, then total number of HLA mismatches is missing. Otherwise the total number of HLA mismatches is the sum of the mismatches from the three loci.

An example following rules 1-4 above is provided below:

Donor:	HLA A		HLA B		HLA DR	
(broad types)	A11	A10	B5	B5	DR5	DR6

Recipient:	HLA A		HLA B		HLA DR	
(broad types)	A10	A19	B12	B5	DR5	DR7

Mismatch:	HLA A	HLA B	HLA DR	Total
	1	0	1	2

9.2 Appendix 2: Futility Analysis

The decision rule for stopping the trial based on efficacy is outlined below:

1. At the interim look, suppose we have cumulative n_i $(i = 0, 1)$ subjects from treatment i ($i = 0$ for placebo and $i = 1$ for vaccine). The cumulative number of subjects with viremia in treatment i will be denoted as s_i $(i = 0, 1)$.
2. The additional number of subjects with viremia at the end of trial could be any integer between 0 and $N - n_i$ for treatment i, where N is the total number of subjects planned for each group. The probability that there are additional k_0 subjects with viremia in the placebo group and k_1 subjects with viremia in the vaccine group at the end of trial is

$$p(k_0, k_1) = \binom{N - n_0}{k_0} \frac{B(\alpha + s_0 + k_0,\ \beta + N - s_0 - k_0)}{B(\alpha + s_0,\ \beta + n_0 - s_0)} \times \binom{N - n_1}{k_1} \frac{B(\alpha + s_1 + k_1, \beta + N - s_1 - k_1)}{B(\alpha + s_1, \beta + n_1 - s_1)} \quad \text{(A)}$$

   where α and β are some arbitrary prior parameters and $B(a, b) = \int_0^1 x^{a-1}(1 - x)^{b-1} dx$ is a beta function. (For this study, we use $\alpha = 0.6, \beta = 0.4$.) The reduction in relative risk is estimated as $rrr = 1 - \frac{s_1 + k_1}{s_0 + k_0}$ with probability (A) above.

3. Sum up the probabilities with which $rrr \geq 25\%$ over all possible values of k_0 and k_1 to get the predictive probability PP:

$$BPP = \sum_{k_0=0}^{N-n_0} \sum_{k_1=0}^{N-n_1} p(k_0, k_1) step(rrr \geq 25\%)$$

   where the $step\ function = 1$ if $rrr \geq 25\%$ and 0 otherwise.

If $BPP \leq cutoff$ then ending the study is indicated. Otherwise the study should be continued. Here the *cutoff* =20% is an empirical value determined by simulation studies.

9.3 Appendix 3: Simulation Studies

The number of incidence *x* has the binomial distribution given the probability parameter π:

$$p(x|\pi) = \binom{n}{x}\pi^x(1-\pi)^{n-x}, \quad x=0, 1, \ldots, n \qquad (1)$$

We assume the distribution for π follows beta distribution with parameters α and β:

$$p(\pi) = Beta(\alpha,\beta) = \frac{1}{B(\alpha,\beta)}\pi^{\alpha-1}(1-\pi)^{\beta-1}, \quad 0<\pi<1 \qquad (2)$$

where $B(\alpha, \beta)$ is a beta function

$$B(\alpha,\beta) = \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha+\beta)}.$$

Then the posterior distribution is a beta distribution as well

$$p(\pi|x) = \frac{p(x|\pi)p(\pi)}{p(x)} \sim \pi^x(1-\pi)^{n-x}\pi^{\alpha-1}(1-\pi)^{\beta-1}$$
$$\sim \pi^{(\alpha+x)-1}(1-\pi)^{(\beta+n-x)-1} = Beta(\hat{\alpha},\hat{\beta}), \quad (3)$$

where $\hat{\alpha} = \alpha + x$ and $\hat{\beta} = \beta + n - x$. This conjugate feature of Beta distribution will be used in the simulations below.

We start with a hypothetical scenario where the viremia incidence rate π_i is known ($i = 0$ for placebo and $i = 1$ for vaccine). Let n_1 and n_2 be the cumulative number of subjects each group has at the first and second interim look, respectively. And let *N* denote the number of subjects each group has at the end of trial.

1. The data at the first interim look will be simulated by drawing $n_1 = 25$ random samples from $binomial(n_1, \pi_i)$ $(i = 0, 1)$. The number of incidence will be denoted as s_{1i} $(i = 0, 1)$.
2. Based on the conjugate feature of the beta prior, the distribution of the viremia incidence rate should be updated to $Beta(\alpha + s_{1i}, \beta + n_1 - s_{1i})$ $(i = 0, 1)$ at the first interim look. Draw *J* random samples for θ_{1i} from the above beta distribution, where θ_{1i} is a random sample of the viremia incidence rate for the *ith* group $(i = 0, 1)$ at the first interim look.
3. For each θ_{1i} draw *M* random samples from $binomial(N - n_1, \theta_{1i})$ to simulate the outcomes at the end of trial when all subjects are recruited and followed up for the endpoint $(i = 0, 1)$. The number of additional (plus) incidence will be denoted as ps_{1i} $(i = 0, 1)$. Consequently, the reduction in relative risk is estimated as $rrr = 1 - \frac{s_{11}+ps_{11}}{s_{10}+ps_{10}}$.
4. Compute the proportion *P* of $rrr \geq 25\%$ over the $J \times M$ random samples. If $P \leq cutoff$, here the cutoff a threshold value (say 20%) to be determined the simulation studies, then stop the study. Otherwise proceed to the step below.

5. Draw additional $n_2 - n_1 = 20$ random samples from $binomial(n_2 - n_1, \pi_i)$ $(i = 0, 1)$. Suppose the number of incidence is s_{2i} $(i = 0, 1)$. The distribution of the viremia incidence rate is now updated to $Beta(\alpha + s_{1i} + s_{2i}, \beta + n_2 - s_{1i} - s_{2i})$ $(i = 0, 1)$ at the second interim look. Draw *J* random samples for θ_{2i} from the above beta distribution, where θ_{2i} is a random sample of the viremia incidence rate for the *ith* group $(i = 0, 1)$ at the second interim look.
6. For each θ_{2i} draw *M* random samples from $binomial(N - n_2, \theta_{2i})$ to simulate the outcomes at the end of trial when all subjects are recruited and followed up for the endpoint $(i = 0, 1)$. The additional number of incidence will be denoted as ps_{2i} $(i = 0, 1)$. The reduction in relative risk is estimated as $rrr = 1 - \frac{s_{11}+s_{21}+ps_{21}}{s_{10}+s_{20}+ps_{20}}$.
7. Compute the proportion *P* of $rrr \geq 25\%$ over the $J \times M$ random samples. If $P \leq cutoff$ then stop the study. Otherwise continue the study to the end when all N subjects are enrolled and followed up for the end point one year after the first injection of study drug.
8. Repeat steps 1-7 *R* times to estimate the probability of stopping the study at first and second looks for a given hypothetical scenario as the proportion of stopping over the *R* repetitions.

We repeat the process for various scenarios. Specifically, the scenarios considered are (1) no effect (incidence rates in the two groups are equal), (2) minor effect (10% reduction in incidence rate), (3) meaningful effect (25% reduction in incidence rate), and (4) significant effect (45% reduction in incidence rate). The incidence rates for placebo group considered are 46% and 51%. For each scenario, we run the simulations with R=1000, J=1000, and M=1000.

Simulation results are presented in the tables below.

Table 1: The cumulative probability of the Bayesian predictive probability (BPP) that the viremia incidence rate is at least 25% lower in ASP0113 than that in placebo is less than 25% (futility) at each interim look for different scenarios.

Viremia incidence rate		**Cumulative probability of futility**			**Prob of success**
Placebo	ASP0113	1st look	2nd look	End of study	End of study
0.51	0.51	0.680	0.921	0.976	0.024
	0.46	0.528	0.827	0.908	0.092
	0.38	0.285	0.520	0.636	0.364
	0.28	0.083	0.155	0.175	0.825
0.46	0.46	0.656	0.882	0.961	0.039
	0.41	0.511	0.766	0.868	0.132
	0.34	0.275	0.510	0.609	0.391
	0.25	0.079	0.172	0.185	0.815

Table 2: The cumulative probability of the Bayesian predictive probability (BPP) that the viremia incidence rate is at least 25% lower in ASP0113 than that in placebo is less than 20% (futility) at each interim look for different scenarios.

Viremia incidence rate		**Cumulative probability of futility**			**Prob of success**
Placebo	ASP0113	1st look	2nd look	End of study	End of study
0.51	0.51	0.632	0.905	0.971	0.029
	0.46	0.474	0.800	0.897	0.103
	0.38	0.247	0.479	0.614	0.386
	0.28	0.064	0.138	0.159	0.841
0.46	0.46	0.608	0.865	0.957	0.043
	0.41	0.454	0.747	0.862	0.138
	0.34	0.246	0.470	0.594	0.406
	0.25	0.059	0.149	0.164	0.836

Table 3: The cumulative probability of the Bayesian predictive probability (BPP) that the viremia incidence rate is at least 25% lower in ASP0113 than that in placebo is less than 15% (futility) at each interim look for different scenarios.

Viremia incidence rate		**Cumulative probability of futility**			**Prob of success**
Placebo	ASP0113	1st look	2nd look	End of study	End of study
0.51	0.51	0.579	0.879	0.966	0.034
	0.46	0.425	0.760	0.885	0.115
	0.38	0.195	0.435	0.590	0.410
	0.28	0.046	0.116	0.141	0.859
0.46	0.46	0.554	0.846	0.954	0.046
	0.41	0.385	0.710	0.850	0.150
	0.34	0.205	0.421	0.567	0.453
	0.25	0.045	0.118	0.137	0.863

When there is no treatment effect (0.46 vs 0.46 or 0.51 vs. 0.51) the BPP $\leq$ 0.25 criterion results in >65% chance to terminate the study; BPP $\leq$ 0.2 criterion results in about 61% chance while BPP $\leq$ 0.1 offers less than 50% chance which is too low to serve our purpose since the goal of the interim analysis is to stop early when there is no treatment effect.

When there is a fair treatment effect (25% reduction in viremia rate) (0.46 vs 0.34 or 0.51 vs. 0.38) the BPP $\leq$ 0.25 criterion results in 30% chance to terminate the study while BPP $\leq$ 0.2 criterion results in about 23% chance.

The chance of mistakenly terminating study at interim for the 0.46/0.25 and 0.51/0.28 scenarios is about 7% to 9% for the 0.2 criterion and >10% for the 0.25 criterion.

Overall, the 0.2 cutoff performs well in terms of stop early when there is no treatment effect and the chance not to kill the study when there is a fair treatment effect.

9.4 Appendix 4: List of the SAP Changes and Rationale

The changes to the approved SAP (15April 2014) that affect the analyses are specified with the rationale in the table below.

SAP Sections	Description	Rationale
5.2 Per Protocol Set (PPS)	Removed.	For a Phase 2 study, this type of analysis where a sizable number of patients are excluded from the PPS classification criteria may provide uninterpretable results.
6.1.2 Secondary Efficacy Endpoints	Removed one of the secondary efficacy endpoint of subject survival through one year.	In order to avoid redundancy as as the mortality is summarized as a part of adverse event summary.
7.1 General Consideration	Specified the analysis duration of the primary study period as data collected through day 380 (=365+14+1) for this SAP.	This analysis duration is specified by taking the protocol allowed visit windows in order to clarify the data inclusion for this analysis plan.
7.2.2 Protocol Deviation	Removed the category of PD5-Other.	In order to capture the protocol deviations to specific categories utilizing PD1 thorugh PD4.
7.4.1.2 Sensitivity Analysis for Primary Efficacy Endpoint	• Clarified the analysis to assume a patient with at least 2 consecutive missing central laboratory viral load as a CMV viremic, and • Added an analysis to consider a patient who took AVT that is adjudicated as a CMV viremia treatment but no evidence of CMV viremia by central laboratory is assumed CMV viremic.	These sensitivity analyses are planned in order to evaluate the robustness of the primary analysis for the primary efficacy endpoint.
7.4.3 Analysis of Exploratory Endpoints	The assessments of kidney transplantation and SF-12 questionnares to be only listed without a formal analysis within this analysis plan.	A proper analysis for these questionnaires to be conducted by the HEOR expert.
7.5.2 Adverse Events of Special Interest	Removed the following AEs of special interest: • Opportunistic infections • Special infections related to kidney transplant • Post-transplant lymphoproliferative disorder	The opportunistic infection is a prespecified exploratory efficacy endpoint thus removed from this section in order to avoid redundency. The second and third bullet items are removed because these events are not expected to occur under vaccine treatment.
7.5.3 Clinical Laboratory Evaluation	Removed the shift summary for laboratory parameters using low, normal and high normal ranges.	The laboratory values are summarized for the change from baseline using the descriptive statististics.

7.5.3 Clinical Laboratory Evaluation	Removed the following: • Potentially clinically significant (PCS) laboratories • Shift tables for SGOT, SGPT, Platelets, Hematocrit, Hemoglobin, Serum creatinine, and Total bilirubin at granular categories	This type of analysis is considered medically not meaningful.
7.5.3.1 Liver Function Test	The criteria are updated to the following: • ALT **or** AST > 3xULN, > 5xULN, > 10xULN, >20xULN • ALT > 3xULN, > 5xULN, > 10xULN, >20xULN • AST > 3xULN, > 5xULN, > 10xULN, >20xULN • ALP > 1.5xULN, >3xULN • Total Bilirubin >2xULN • ALT **or** AST > 3xULN **and** Total Bilirubin > 1.5xULN • ALT **or** AST > 3xULN **and** Total Bilirubin > 2xULN • ALT **or** AST > 3xULN **and** ALP< 2xULN **and** Total Bilirubin > 2xULN	These new criteria are the sponsor's standard categories.
7.5.4 Vital Signs	Removed the summary of potentially significant vital signs based on special criteria.	The vital sign is summarized for the mean change from baseline using the descriptive statistics.
7.8 Subgroups of Interest	Removed the subgroup analysis on adverse events of special interest for the various subgroup factors.	This type of subgroup analysis on potentially small number of patients with AEs of special interest may yield uninterpretable results.

9.5 Appendix 5: Signatures

Prepared by: _____ Date: _____

[redacted], Ph.D

Date (DD Mmm YYYY)

Approved by: _____ Date: _____

[redacted], Ph.D

Date (DD Mmm YYYY)

_____ Date: _____

[redacted], M.D.

Date (DD Mmm YYYY)

_____ _____

[redacted], M.D.

Date (DD Mmm YYYY)

_____ Date: _____

[redacted]

Date (DD Mmm YYYY)