A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seropositive Recipients Undergoing Allogeneic, Hematopoietic Cell Transplant (HCT)

ISN/Protocol 0113-CL-1004

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

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Northbrook, IL 60062

STATISTICAL ANALYSIS PLAN

Final Version 3.0, dated 19-May-2017

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
aGVHD	Acute Graft-versus-host Disease
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ASP0113	DNA vaccine being tested in this study
AST	Aspartate Transaminase
ATG	Anti-thromocyte Globulin
AVT	Antiviral Therapy
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BMTS	Bone Marrow Transplantation Subscale
cGVHD	Chronic Graft-versus-host Disease
CI	Confidence Intervals
CIF	Cumulative Incidence Function
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EOD	End Organ Disease
EQ-5D	EuroQol – 5D
FACT-BMT	Functional Assessment of Cancer Therapy – Bone Marrow Transplant
FAS	Full Analysis Set
FDA	Food and Drug Administration
gB	Glycoprotein B
GVHD	Graft-versus-host Disease
H_0	Null Hypothesis
H_1	Alternative Hypothesis
HCT	Hematopoietic Cell Transplant
HCT-CI	Hematopoietic Cell Transplant Comorbidity Index
HEA	Health Economics Assessment

Abbreviations	Description of abbreviations
HECOR	Health Economics and Clinical Outcomes Research
HLA	Human Leukocyte Antigen
HLT	High-Level Term
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IRT	Interactive Response Technology
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
mL	Milliliter
m^2	Meter squared
mm^3	Millimeter cubed
mmHg	Millimeters of Mercury
mSAF	Modified Safety Analysis Set
NCI-CTCAE	National Institutes of Health Common Terminology Criteria for Adverse Events
PD	Pharmacodynamics
PE	Physical Examination
PGx	Pharmacogenomics
PK	Pharmacokinetic
pp65	Phosphoprotein 65
PPS	Per Protocol Set
PT	Preferred Term
QOL	Quality of Life
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment emergent Adverse Event
TLF	Tables, Listing, and Figures
ULN	Upper Limit of Normal
VE	Vaccine Efficacy
WHO-DRL	World Health Organization Drug Reference List
WPAI: GH	Work Productivity and Activity Impairment Questionnaire: General Health

List of Key Terms

Terms	Definition of terms
Adverse Event	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.
Baseline	The last measurement / evaluation on or prior to the first dose of randomized therapy is considered the baseline measure/evaluation.
Censored Data	The value of a measurement or observation which is only partially known, such as an event has not yet happened at the time of loss of contact before the study is completed.
CMV Infection	Replication of CMV (isolation of the virus or detection of viral protein or nucleic acid in any body fluid or tissue).
CMV Viremia	Presence of CMV in the blood.
End of Study in Primary Study Period	The point in time when the last protocol-defined assessment has been completed in the primary study period (excludes 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.
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.
Long-term Follow-up Period	The period of time from the Day 365 Visit (Visit 14) through the completion of the 4½ year additional safety follow-up.
Preemptive Therapy	A therapeutic treatment regimen where treatment for an infection/disease is initiated only after it is detected/confirmed.
Primary Analysis Period	The time between the first dosing of study drug through 1 year post transplant
Primary Study Withdrawal	A subject who is randomized but does not complete the Primary Study Period for any reason.
Prophylactic Therapy	A therapeutic treatment regimen where treatment is 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 between days -3 to -14 prior to the transplant date.
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.
Treatment Emergent Adverse Events for SAP	Adverse events occurring after the first dose of study drug and up to 1 year post-transplant.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis that is described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

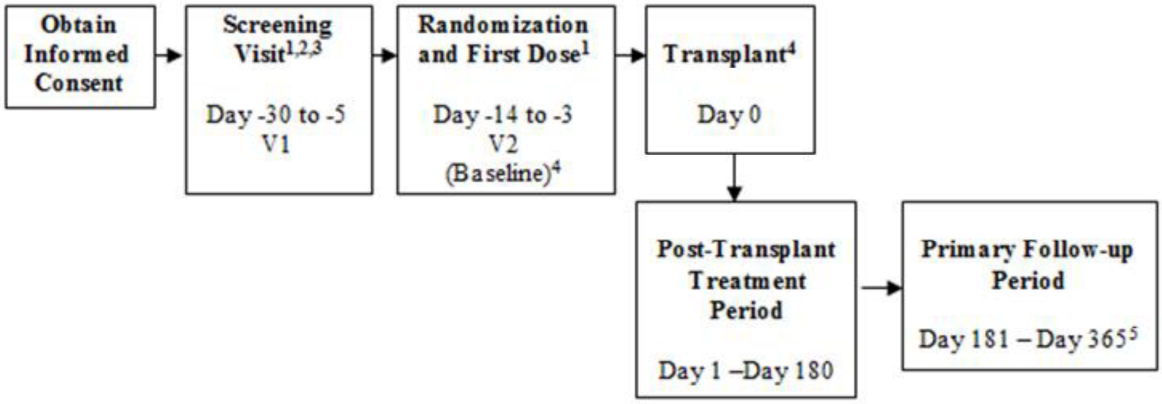
The SAP is finalized and signed prior to study unblinding. The list of changes from the Final Version 2.0 that affect the analysis is documented in Section 8.

Any analytical changes from the final version of the SAP will be documented in the Clinical Study Report (CSR).

2 FLOW CHART AND VISIT SCHEDULE

Flow Chart

Primary Study Period: Screening/ICF through 12-months Post-Transplant (Day 365/Visit 14)



1. Screening visit and V2 (first dose) may occur either separately or on the same day. Eligibility will be determined using local laboratory results collected at the screening visit. The first dose of study drug must be administered prior to conditioning therapy. The dosing interval in relation to transplant/conditioning must be maintained.
2. Local laboratory assessments may be repeated 1 time if abnormal within the 25 day screening period.
3. The subject may be rescreened 1 time if the transplant is delayed and it will be outside the 25 day screening window. If outside the 25 day screening period, all screening procedures must be repeated.
4. Baseline is date of first dose (V2). The day of transplant (donor cell infusion) is day 0 and all visit days are relative to day 0.
5. Note that the day 365 visit must occur on day 365 +14 days (between day 365 to 379); it cannot occur prior to day 365.

Table 1 Schedule of Assessments – Primary Study Period Visit 1 (Screening) – Day 365

	Screening[2]	Dose 1[17] (Baseline)		Transplant[20]	Dose 2		Dose 3		Dose 4			Dose 5			Primary Study Period Completion / Early Termination Visit25
Visit Number	**V1[4]**	**V2[4]**	**V3[20]**	**V4**	**V5[24]**	**V6[24*]**	**V7**	**V8**	**V9**	**V10***		**V11**	**V12***	**V13**	**V14**
Day Relative to Transplant or Prior Dose	-30 to -5	-14 to -3	Follow-up Dose 1 +10 to 14 days	0	14-40	Follow-up to Dose 2 +10 to 14 days	60	Follow-up to Dose 3 +10 to 14 days	90	Follow-up to Dose 4 +10 to 14 days	100	180	Follow-up to Dose 5 +10 to 14 days	270	365
Visit Window							±5 days		±10 days			±10 days		±10 days	+ 14 days (between Day 365 to 379)
Month	-1			0	1		2		3			6		9	12
Assessments															
Informed Consent[1]	X														
Subject Number Assignment[3]	X														
Inclusion/Exclusion Assessment	X	X^P													
Medical History & Demographics	X	X^P													
Clinical Evaluation (Physical Exam & Vitals)[5]	X	X^P			X^P		X^P		X^P			X^P		X	X
Concomitant Medication Review[6]	→	→	→	→	→	→	→	→	→	→	→	→	→		
Safety Laboratory[7]	X	X			X^P	X	X^P	X	X^P	X		X^P	X		
CMV Screening Serology[8]	X														
Modified HCT-CI Score[9]	X														
Pregnancy Test (females)[10]	X	X^P			X^P		X^P		X^P			X^P		X	X
Adverse Event and SAE Review[11]	→	→	→	→	→	→	→	→	→	→	→	→	→		
Randomization		X^P													
Health Economic Assessment (HEA)	→	→	→	→	→	→	→	→	→	→	→	→	→		
EQ-5D, FACT-BMT, WPAI[12]		X^P			X^P		X^P		X^P			X^P		X	X
Immunogenicity Laboratory[13]		X^P			X^P			X	X^P			X^P			X

Table continued on next page

	Screening[2]	Dose 1 [17] (Baseline)		Transplant[20]	Dose 2		Dose 3		Dose 4			Dose 5			Primary Study Period Completion / Early Termination Visit25
Visit Number	**V1[4]**	**V2[4]**	**V3[20]**	**V4**	**V5[24]**	**V6[24*]**	**V7**	**V8**	**V9**	**V10***		**V11**	**V12***	**V13**	**V14**
Day Relative to Transplant or Prior Dose	-30 to -5	-14 to -3	Follow-up Dose 1 +10 to 14 days	0	14-40	Follow-up to Dose 2 +10 to 14 days	60	Follow-up to Dose 3 +10 to 14 days	90	Follow-up to Dose 4 +10 to 14 days	100	180	Follow-up to Dose 5 +10 to 14 days	270	365
Visit Window							±5 days		±10 days			±10 days		±10 days	+ 14 days (between Day 365 to 379)
Month	-1			0	1		2		3			6		9	12
Platelet count[14]		X[P]			X[P]		X[P]		X[P]			X[P]			
Pharmacogenomics (PGx) – (Optional)[15]		X[P]													
CMV Plasma Viral Load Testing[16]				Start Weekly Testing; See Table 1a							Every Other Week		Every 30 days		
Study Drug Injection[17]		X[17]			X		X		X			X			
Local Reactogenicity Assessment[18, 19]		X			X		X		X			X			
Transplant Information[21]				X											
DONOR Blood Sample (Optional)[22]				X											
Karnofsky Performance Scale		X			X		X		X			X		X	X
aGVHD and cGVHD[23] (See Table 1a)					X		X		X			X		X	X

P = procedure to be completed prior to dosing *= Visit procedures may be performed by Home Health Care (HHC), if applicable in the country. Note: When CMV Plasma Viral Loads fall outside of a regular clinic Visit, the blood draw may be performed by HHC.

CMV Plasma Viral Load Testing (Central Laboratory) and GVHD Assessments

Assessment Number	V4 Transplant	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17	A18	A19	A20	A21	A22	A23	A24	A25
	Day 0	Day 7 Week 1	Day 14 Week 2	Day 21 Week 3	Day 28 Week 4	Day 35 Week 5	Day 42 Week 6	Day 49 Week 7	Day 56 Week 8	Day 63 Week 9	Day 70 Week 10	Day 77 Week 11	Day 84 Week 12	Day 91 Week 13	Day 98 Week 14	Day 112 Week 16	Day 126 Week 18	Day 140 Week 20	Day 154 Week 22	Day 168 Week 24	Day 198	Day 228	Day 258	Day 288	Day 318	Day 348
Visit Window (days)		±4	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
CMV[16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
aGVHD[23]		X	X	X	X	X	X	X	X	X	X	X	X	X	X											

Note: When CMV Plasma Viral Loads fall outside of a regular clinic visit, the blood draw may be performed by HHC.

1. Informed consent must be obtained prior to the performance of any study-related procedure and before randomization.
2. Screening procedures may be completed -30 to -5 days prior to the day of transplant. Local laboratory results are to be used for screening purposes. The screening laboratory results may be repeated 1 time throughout the noted period. The subject may be rescreened 1 time if the transplant is delayed and it will be outside the 25 day screening window. If outside the 25 day screening period, all screening procedures must be repeated.
3. Subjects will be assigned a subject number for use throughout the study at the screening visit via the Interactive Response Technology (IRT) system.
4. Screening visit and V2 (first dose of study drug) may occur either separately or on the same day.
5. A complete physical examination (PE) will be conducted at the screening (V1) and at the primary study period completion/day 365 visit (V14). At all other visits where a PE is performed, symptom-directed PEs may be done. A detailed description of the subject's current disease status and conditioning regimen (including doses) will be recorded at the baseline visit (V2). The evaluations conducted at each visit are to be performed by the Investigator or qualified medical personnel who routinely perform these evaluations in this subject population. Vital signs will be collected immediately prior to injection and 60 (±10) minutes post injection (except weight) at study visits accompanied by injection and once at screening (V1), and at V13 & 14. Vital signs include blood pressure, pulse rate, respiratory rate, temperature and weight. Height will be collected at the screening visit. Performance status will be assessed using the Karnofsky Performance Scale (KPS) at baseline visit (V2).
6. All concomitant medications and therapies administered from 30 days prior to transplant through 30 days post last dose of study drug will be collected on the electronic case report form; Concomitant medications and therapies associated with Grade 3 and higher grade adverse events (AEs) as well as all serious adverse events (SAEs) will be collected from 31 days post last dose of drug through 1 year post-transplant. Over-the-counter medications, and herbal remedies do not need to be captured beginning 30 days after the last dose of study drug.

Footnotes continued on next page

7. Safety Laboratory will be drawn at the screening visit using the local laboratory. Safety laboratory will be done by a central laboratory at baseline, before doses 2-5, and at each follow-up time point for doses 2-5, and will include hematology and biochemistry, including a hepatic profile. Please refer to [Protocol Appendix 1] for a full list of routine safety parameters that will be tested, and to [Protocol Section 5.4.3] and the Laboratory Manual for further instruction on laboratory collection and processing.
8. Screening for cytomegalovirus (CMV) immunoglobulin G (IgG) seropositivity by the local laboratory may be performed up to 30 days prior to transplant and before randomization.
9. The modified hematopoietic cell transplant-comorbidity index (HCT-CI) score are to be completed during screening with history and laboratory from the screening visit. Local laboratory results are to be used in the assessment. Local laboratories may be repeated once to score the HCT-CI. Pulmonary function tests (PFTs) including forced expiratory volume (FEV1) and diffusing lung capacity of carbon monoxide (DLco), multi gated acquisition scan (MUGA), and/or echocardiograms performed within 6 months (180 days) prior to screening are to be used for scoring pulmonary and cardiac comorbidities. PFTs (FEV1 and DLco), MUGAs /or echocardiograms not performed within 6 months of screening will have to be repeated for scoring purposes.
10. For all females of childbearing potential, a urine or serum pregnancy test will be performed at screening, on the same day and prior to each dose, at visit 13, and at the primary study period completion/day 365 visit (V14). All pregnancy tests will be done locally. For subjects who receive mycophenolate mofetil, additional pregnancy testing should be done in accordance with local regulatory requirements.
11. All AEs and SAEs will be collected from signing of the informed consent through 30 days post last dose of study drug. All events requiring adjudication (CMV end organ disease [EOD], initiation of CMV-specific antiviral therapy [AVT], and cause of death), grade 3 and higher grade AEs as well as all SAEs will be collected from 31 days post last dose of drug through 1 year post-transplant. A change in medical status or medical history from time of signing of informed consent through first dose of study drug is to be reported as an AE or SAE as applicable. In this study, the day 0 HCT is not considered an AE.
12. The EuroQol – 5D (EQ-5D), Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT), and Work Productivity and Activity Impairment Questionnaire (WPAI) are to be completed by the subject prior to any other study assessments or visit procedures. Subjects are to complete these assessments in the following order: EQ-5D first, FACT-BMT second, WPAI:GH last. For all 3 patient-reported outcome measures, i.e. EQ-5D, FACT-BMT, WPAI, 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 a question, the rest of the questionnaire still needs to be completed.
13. Immunogenicity laboratories include collection of blood for the glycoprotein B (gB) antibody and phosphoprotein 65 (pp65) T-cell assays. Samples are to be drawn on visits V2, V5, V8, V9, V11 and V14. Samples for T-cell assays will not be collected if the absolute lymphocyte count is known to be < 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.
14. The platelet count must be at least ≥ 50000 mm^3 (spontaneously or after platelet transfusion) performed by the local laboratory within 3 days prior to all study drug injections. Prior to all study drug injections, confirmation must be made that there is no medical contraindication to an IM injection. Results received in an equivalent local unit of measure must be converted to SI units. If the subject's platelet count does not meet this threshold at the time of the visit, the subject may return for the study drug injection and local reactogenicity assessment at a later time within the allowable window for the visit. If the subject's platelet count does not meet this threshold during the visit window, the dose must be skipped and the corresponding follow-up safety laboratory and reactogenicity assessment should not be done. The second injection should be given as close to, but not prior to, day 14 as possible.
15. Subjects who consent to participate in the pharmacogenomics (PGx) substudy will have a saliva sample collected during the baseline visit (V2), after randomization but prior to the first dose of study drug.

Footnotes continued on next page

16. Plasma viral load by the central laboratory will be monitored weekly (± 2 days) during days 0-100, every other week (±5 days) during days 101-180, every 30 days (±5 days) during days 181-365, at the initiation of CMV-specific AVT, when clinically indicated, and every time a viral load sample is sent to the local laboratory. When CMV-specific AVT is initiated, a central CMV viral load will be obtained a minimum of weekly until CMV-specific AVT is discontinued. Thereafter, the regularly scheduled viral load assessments will resume according to the scheduled protocol assessments.
17. The first dose is to be given at day -14 to -3 prior to transplant and within 72 hours prior to the start of chemotherapy and radiation therapy for conditioning.
18. The subject must be monitored directly for the first 15 minutes of the injection. The subject must be in the clinic, but does not require direct monitoring, from 15 minutes through 1 hour after the injection.
19. Local reactogenicity will be evaluated 1 hour (± 10 minutes) after each injection and for each of the 7 consecutive days following each injection beginning approximately 24 hours following each dose (day 1-7 postdose). The assessments for each of the 7 consecutive days following an injection will be done by the subject and reported to the site via diary. When reactogenicity is reported as an AE, it is to be followed until resolution or medically stable. All local reactions ≥ grade 3 (Protocol Appendix 7) require confirmation by a health care professional.
20. The date of transplant (donor cell infusion) defines day 0 and all visit days are relative to day 0. Based on this schedule, V3 may occur prior to or after the day of transplant, day 0.
21. Transplant information includes recipient transplant volume infused, HLA typing of the donor and recipient, HLA cross match at time of transplant (as determined by the site's standard method of determination and, if available), type of transplant, the number of CD34+ stem cells/kg infused if available, donor and recipient CMV serostatus, if available the hepatitis B virus (HBV) serostatus, hepatitis C virus (HCV) serostatus, and Epstein Barr Virus (EBV) serostatus of the donor and recipient; blood type of the donor and recipients. ABO cross match (if available), donor-recipient relatedness, donor gender, age, race (if available) and ethnicity (for the USA only and if available); donor product plasma, volume and RBC depletion status; and if available donor cell product CD3+, CD4+, CD8+ and CD56+ cell counts. For bone marrow recipients, the number of mononuclear cells transfused must also be included, if possible.
22. *Optional*: A 20 mL peripheral blood sample from the CMV seropositive donors will be obtained prior to the stem cell donation for recipients participating in the main trial to test for CMV-specific T-cells (requires donors' consent). For those donating peripheral stem cells, the donor blood sample is to be collected prior to the initiation of mobilization therapy (e.g., G-CSF). Not applicable to sites in Japan.
23. Acute and chronic GVHD is to be assessed and graded/globally scored and the KPS will be used to assess performance status at baseline and V5, V7, V9, V11, and V13 following transplant (day 0) through the primary study period completion/day 365 visit (V14) except when the visit is conducted by HHC. In addition, aGVHD needs to be assessed weekly through day 100. When a diagnosis of aGVHD is made for a subject, assessments are to continue weekly until resolution for maximal grade and stage by key organs. Local laboratories may be used for staging. When a diagnosis of cGVHD or aGVHD is made by a health care professional for a subject, the subject should return to the study center for evaluation and data collection, and assessments are to be done at each regularly scheduled protocol visit until resolution; the maximum score during the interval from the last assessment to the current assessment is to be recorded for assessments performed at the study site.
24. If the subject does not meet the criteria for dosing by day 40, V5 procedures (except study drug injection and local reactogenicity assessment) need to be completed within 5 days of day 40 (day 40 to 45) and V6 should be skipped.
25. The day 365 visit must occur on day 365 +14 days (between day 365 to 379); it cannot occur prior to day 365 for subjects who do not prematurely withdraw from both treatment and continued follow-up. For a subject who prematurely withdraws from the study (discontinues treatment with no continued follow-up), the study completion visit is to be completed within 14 days of study withdrawal.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objectives

- To evaluate the efficacy of ASP0113 compared with placebo as measured by a primary composite endpoint of overall mortality and CMV end organ disease (EOD) through 1 year post-transplant.
- To evaluate the safety of ASP0113 in subjects undergoing allogeneic HCT.

3.2 Study Design

Study 0113-CL-1004 is a Phase 3 randomized, double-blind, placebo-controlled trial. Randomized subjects will receive 5 injections of either ASP0113 or placebo in the following 5 periods where the days are relative to the day of transplant (Day 0): Days -14 to -3, 14 to 40, 60 ±5, 90 ±10 and 180 ±10. The first study drug injection will be given on the same day as, but prior to, the start of chemotherapy and radiation therapy for conditioning and the second injection should be given as close as possible to, but not prior to, Day 14. All study drug injections will be administered only when the platelet count is $\geq$ 50000 mm^3 (spontaneously or after platelet transfusion) and when there is no medical contraindication to an intramuscular (IM) injection.

3.3 Randomization

At the Screening Visit, after the Informed Consent Form (ICF) has been signed, the subject receives a subject number assignment through the IRT for use throughout the study.

Subjects who subsequently meet all inclusion and none of the exclusion criteria will be randomly assigned to receive either ASP0113 or placebo. The randomization to treatment groups will be equally allocated in a 1:1 ratio and stratified by donor-recipient relatedness and donor CMV serostatus.

The IRT vendor generates the randomization schedule. To obtain the randomized treatment assignment for a subject, the pharmacist or designee utilizes an IRT, which is available 7 days a week, 24 hours a day.

Randomization is done after the completion of the Screening period, and at least 14 to 3 days prior to the anticipated transplant day (Day 0). After submitting required information about the eligible subject, the drug kit number assignment is provided. Study drug assignment remains blinded to all site staff except the pharmacist and designated staff.

Randomization of subjects will continue until approximately 500 subjects have been received at least 1 dose of the study. Subjects who discontinue the study early after receiving the first dose of study drug will not be replaced.

4 SAMPLE SIZE

In the primary analysis set of a Phase 2 study of the efficacy of ASP0113 in HCT, 7 subjects died and 2 additional subjects experienced CMV EOD out of 40 treated with ASP0113, for

an overall failure rate of 22.5%, while among the placebo subjects 11 subjects died and 1 additional subject experienced CMV EOD out of 34, for an overall failure rate of 35.3%.

To detect the estimated difference in mortality and CMV EOD from the phase 2 study (35.3% vs. 22.5%), the study needs a sample size of at least 424 (212 per arm) to have 80% power at the 2-sided significance level of 0.050. A trial of size 500 (250 per arm) is expected to have 86% power for the composite endpoint.

All calculations used nQuery Advisor 7.0, procedure PPT1 [2 group continuity corrected χ^2 test of equal proportions (odds ratio = 1) (equal n's)] with the assumptions described above.

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 is for the data that is included for the primary analysis period which is defined as 1-year period from the transplantation for the efficacy assessment while the safety analysis will be analyzed from the first study drug injection. Certain data summaries will consider the analysis windows as specified in the relevant sections. The analysis for the long-term follow up data will be developed in a separate SAP.

5.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized subjects who receive at least 1 dose of randomized study drug. Subjects will be included in analyses using the FAS based on assigned treatment. Summaries of demographic and baseline characteristics will be provided for the FAS and the FAS will also be used for efficacy analyses.

5.2 Modified Full Analysis Set

The Modified Full Analysis Set (mFAS) will consist of all subjects in the FAS, except for 68 subjects who were included in the first time futility analysis. Summaries of demographic and baseline characteristics will be provided for the mFAS, and the mFAS will also be used for efficacy analyses.

5.3 Per Protocol Set

The Per-Protocol Set (PPS) includes subjects from the FAS who do not meet the prespecified PPS exclusion criteria as listed in Section 5.3.1 of this SAP.

The allocation of subjects to the PPS will be determined prior to database unblinding. An independent document for the Classification Specifications will be developed and signed. Final judgments on exclusion of subjects from the PPS will be made at the blinded data review meeting (BDRM), which will be held prior to treatment unblinding.

The PPS set may be utilized for efficacy analyses applied to both FAS and mFAS, as appropriate.

5.3.1 Reasons for Exclusion From PPS

The following reasons may lead to a subject's exclusion from PPS:

- Did not undergo HCT.
- Received different study drug injection from randomized, or study drug is switched during the study
- Administration of prohibited concomitant treatment as described in the Study Protocol.
- Violation of the following inclusion or exclusion criteria which may affect the assessment of the efficacy of the study drug:
    - Inclusion criterion No 3, subject was CMV-seropositive HCT recipient as confirmed by local laboratory at screening.
    - Inclusion criteria No 4 and 5, subject did not undergo 1 of the procedures indicated in these inclusion criteria.
    - Inclusion criterion 6, subject did not have any of the indicated underlying conditions.
    - Inclusion criterion 13, subject participated in another interventional study while on treatment.
    - Exclusion criterion No 1, subject had active CMV disease or infection or had received treatment for active CMV disease or infection within 3 months (90 days) prior to transplant.
    - Exclusion criterion No 6, subject received any of the following substances or treatments:
        - Alemtuzumab within 60 days prior to transplant, including conditioning regimen.
        - T-cell depletion of donor cell product.
        - Administration of a CMV vaccine, including any prior exposure to ASP0113.
    - Exclusion criterion No 7, subject received an allogeneic stem cell transplant within 1 year prior to transplant.
    - Exclusion criterion No 12, subject received a prior HCT and had residual cGVHD.

5.4 Safety Analysis Sets

The Safety Analysis Set (SAF) consists of all randomized subjects who received at least 1 dose of study drug injection. Subjects will be included in the treatment group that the subject received as first injection.

There will be 2 additional safety analysis sets. The Modified Safety Analysis Set (mSAF) will consist of all subjects in the SAF excluding the 68 subjects who were included in the first futility analysis. Another additional safety set will consist of the 68 excluded subjects and will be notated as xSAF.

5.5 Pharmacokinetics Analysis Set (PKAS)

Pharmacokinetics are not applicable to this study.

5.6 Pharmacodynamic Analysis Set (PDAS)

Pharmacodynamics are not applicable to this study.

5.7 Immunogenicity Analysis Set

The Immunogenicity Analysis Set (IAS) will include subjects who received at least 1 dose of randomized study drug and for whom at least 1 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

The primary efficacy endpoint is the proportion of patients with composite of all-cause mortality and adjudicated CMV EOD through 1 year post-transplant.

6.1.2 Secondary Efficacy Endpoints

6.1.2.1 Key Secondary Efficacy Endpoints

The 2 key secondary efficacy endpoints are:

- Time to first protocol-defined CMV viremia through 1 year post-transplant. CMV viremia is defined in the study protocol as CMV plasma viral ≥1000 IU/mL as assessed by the central laboratory.
- Time to first use of adjudicated CMV-specific AVT after study drug first injection through 1 year post–transplant.

6.1.2.2 Other Secondary Efficacy Endpoints

Additional secondary efficacy endpoints are:

- Proportion of patients with a composite endpoint of CMV viremia and CMV-specific AVT use per the adjudication committee
- Time to first event of either use of CMV-specific AVT or diagnosis of CMV EOD after study drug first injection through one year post-transplant. This endpoint is a composite endpoint based on the independent adjudication committee assessments of CMV-specific AVT and CMV EOD.
- All-cause mortality at 1 year post-transplant

6.1.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include the following efficacy outcomes.

- Clinical outcomes:
    - Composite endpoint of all-cause mortality and adjudicated CMV EOD at 6 months post-transplant
    - All-cause mortality at 6 months post-transplant

  - Incidence of adjudicated CMV EOD
  - Incidence of investigator-reported CMV EOD
  - Incidence of grade 3-4 aGVHD
  - Incidence of grade 3 treatment emergent viral, bacterial, or fungal infections other than CMV
  - Maximum grade of aGVHD
  - Relapse mortality (death due to relapse of the subject's primary disease)
  - Non-relapse mortality (death due to causes unrelated to the subject's primary disease)
  - Incidence of engraftment (Yes/No)
  - Incidence of graft rejection/poor graft function
  - Incidence of relapse of primary disease requiring therapy
  - Number of episodes of protocol-defined CMV viremia [CMV plasma viral load ≥ 1000 IU/mL by the Abbott RealTime CMV assay as assessed by the central laboratory]
  - Association between CMV viremia and mortality
- Duration of hospitalization(s), in days:
  - Total duration of ICU stays
  - Total duration of stays in step down units
  - Total duration of stays in hospital general medical/surgical ward
  - Total duration of all hospitalizations
- Total number of days in emergency room and total number of visits to emergency room

Death will be classified as relapse mortality (adjudication CRF indicates 'Death due to relapse of persistent disease') or non-relapse mortality ('Death not due to relapse of persistent disease') by a blinded adjudication committee. If a death has not been adjudicated (e.g., discovered through public records search without a corresponding adverse event) then it will not be considered in either the relapse or the non-relapse mortality analyses.

In determining the number of episodes of protocol-defined CMV viremia, an episode will be considered to start when a viral load is load ≥1000 IU/mL and previous viral loads are <1000 IU/mL. An episode will be considered to end when 2 consecutive viral loads < 1000 IU/mL separated by at least 1 week are observed.

Treatment emergent infections are those occurring after the first dose of study drug and up to 1 year post-transplant.

Total duration of hospitalization will be the sum of hospitalization days added up over all the hospitalizations experienced by a subject within 1 year after transplantation, and will include days in intensive care, step down units and general medical/surgical wards. For comparing treatments, total duration of hospitalization will be normalized to days of hospitalization per year by dividing number of hospitalization days by the number of days of follow-up (starting from day of transplantation), times 365. For example, if a subject has a 3-day hospitalization and a 5-day hospitalization, and is lost to follow-up at 64 days post-transplant, then the value of 45.625 days/year will be used for this subject (365 x 8 / 64 = 45.625).

The same method of normalization will be used for total duration of stays in ICUs, total duration of stays in step down units, total duration of stays in hospital general medical/surgical ward, and total number of emergency room days. The number of emergency room visits will not be normalized.

6.1.3.1 Hospitalizations, Health Economic, and Quality of Life Variables

Health economics and clinical outcomes research variables include the following. Further analyses of these endpoints will be described in a separate SAP.

- Subjects' quality of life variables
    - EuroQol (EQ-5D) dimensions
        - Mobility
        - Self-Care
        - Usual Activities
        - Pain/Discomfort
        - Anxiety/Depression
    - Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT)
    - Work Productivity and Activity Impairment Questionnaire: General Health (WPAI: GH)
- Health Economic Assessment (HEA)

The EQ-5D, FACT-BMT and WPAI: GH are assessed at each dosing visit, at V13 and at the Primary Study Period Completion/Day 365 Visit (V14). Information about administration of these assessments can be found in the study protocol.

Health economic information will be collected for subjects through the Primary Study Period Completion/Day 365 Visit (Visit 14).

6.1.3.1.1 Health Economic Assessments

Health Economic Assessments will include the following: concomitant medications and procedures, hospitalizations, nonscheduled clinic visits and emergency room visits. 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).

6.1.3.1.2 EuroQol (EQ-5D)

The EQ-5D is an international standardized non-disease-specific (i.e., generic) instrument for describing and valuing 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 EQ-5D has 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has 5 response levels (e.g., 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems,

5=extreme problems). In addition, it has a visual analogue scale that elicits a self-rating by the respondent of his/her health status.

6.1.3.1.3 Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT)

The Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) is a self-administered instrument designed to assess multi-dimensional aspects of QOL in bone marrow transplant (BMT) patients. It consists of the 27-item FACT-General (FACT-G) and the 23-item Bone Marrow Transplantation Subscale (BMTS). The FACT-G assesses 4 primary dimensions of QOL, including physical well-being (7 items), social-family well-being (7 items), emotional well-being (6 items) and functional well-being (7 items). A 5-point response scale ranging from 0 to 4 is used (0 = 'not at all'; 1 = 'a little bit'; 2 = 'somewhat'; 3 = 'quite a bit'; and 4 = 'very much').

6.1.3.1.4 Work Productivity and Activity Impairment Questionnaire: General Health (WPAI: GH)

The Work Productivity and Activity Impairment Questionnaire: General Health (WPAI: GH) is a 6-question instrument designed to assess the effect of health problems (physical or emotional problem or symptom) on an individual's ability to work and perform regular activities [see Protocol Appendix 16]. The WPAI: GH is assessed at each dosing visit, at V13 and at the Primary Study Period Completion/Day 365 Visit (V14).

Questions of the WPAI: GH are as follows.

1. Are you currently employed (working for pay)?

2. During the past 7 days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

3. During the past 7 days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

4. During the past 7 days, how many hours did you actually work?

5. During the past 7 days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

6. During the past 7 days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the

amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

If the answer to Question 1 is "No", Questions 2 through 5 are skipped. The answers to Questions 2, 3, and 4 are given in hours. If the answer to Question 4 is "No", Questions 5 is skipped. Question 5 is answered by circling a number from 0 to 10, with 0 representing "Health problems had no effect on my work" and 10 representing "Health problems completely prevented me from working". Question 6 is likewise answered by circling a number from 0 to 10, with 0 representing "Health problems had no effect on my daily activities" and 10 representing "Health problems completely prevented me from doing my daily activities".

WPAI: GH outcomes are expressed as impairment percentages, with higher numbers indicating worse outcomes, as follows.

Q1 = currently employed.

Q2 = hours missed due to health problems.

Q3 = hours missed other reasons.

Q4 = hours actually worked.

Q5 = degree health affected productivity while working.

Q6 = degree health affected regular activities.

If Q1 = 'Yes' then the following are calculated.

Percent work time missed due to health = 100% x Q2/(Q2+Q4).

Percent impairment while working due to health = 100% x Q5/10.

Percent overall work impairment due to health

= 100% x Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4))x(Q5/10)].

If Q1 = 'No' then the above quantities should be considered missing values.

For all subjects, the following will be calculated.

Percent activity impairment due to health = 100% x Q6/10.

6.1.4 Immunogenicity Variables

An indicator of immunogenicity elicited by the vaccine is expected to be an increase in Gb-specific antibody levels and the T-cell response to the 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:

On Visits V2, V5, V8, V9 and V11 and V14:

- 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.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature and weight).
- Adverse events using the NCI-CTCAE v. 4.03 grading scale.
- Acute and non-acute Local reactogenicity signs and symptoms using the protocol-specified reactogenicity scales, as described in Appendix 7 of the study protocol.
- Clinical laboratory assessments.
- Physical examinations.
- Treatment emergent adverse events (TEAEs; frequency, severity, seriousness and relationship to study drug).

Per protocol, All AEs and SAEs will be collected from signing of the ICF through 30 days post last dose of study drug. All events requiring adjudication, Grade 3 and higher AEs and SAEs will be collected from 31 days post last dose of drug through 1 year post-transplant. TEAE is defined as an adverse event observed on the day or after the first injection up to 1 year post-transplant. If the adverse event occurs on the day of the first injection of study drug and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank in eCRF, then the adverse event will be considered treatment emergent. If the adverse event occurs on the day of the first injection of study drug 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 both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date).

The definition of TEAE for this SAP includes adverse events through 1 year post-transplant, regardless of the date of last study medication, rather than only 30 days after the last dose of study medication. This is because, as noted above, all events requiring adjudication, Grade 3 and higher AEs and SAEs are collected through 1 year post-transplant. A drug-related TEAE is defined as any TEAE with possible or probable relationship to study treatment as assessed by the investigator. Any AE with a missing relationship per the investigator will be counted as study drug related AE in the summary.

Any AE with a missing severity per the investigator will be counted as severe, and any AE with a missing seriousness per the investigator will be counted as serious.

Astellas 'Always Serious AE' are identified by Astellas and then queries are issued to the Investigator to consider upgrading the event to serious. If the investigator agrees to upgrade, then the site submits an SAE form for the event and adds the SAE number to RAVE. If they do not agree to upgrade the event, then only the SAE number is entered into RAVE. If an AE has an SAE number on RAVE it is considered Serious even if not indicated as such on the AE record.

6.3 Pharmacokinetic Variables

Pharmacokinetics will not be analyzed in this study.

6.4 Pharmacodynamic Variables

Pharmacodynamics will not be analyzed in this study.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

All statistical analyses and summary information will be generated according to this statistical analysis plan. Any analytical deviations from this plan will be documented in the clinical study report. All numerical rounding should be performed at the end of calculations. The p-values will be displayed with 3 significant digits. 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 (SD), 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 data (i.e., will add up to 100%).

The analyses with the randomization stratification factors, donor-recipient relatedness (Related/Non-related) and donor CMV serostatus (Positive/Negative), that are used in the analyses will be based on the data from IRT.

All statistical comparisons will be made using 2-sided tests at the α=0.05 significance level unless specifically stated otherwise.

The analysis day will be calculated from the day of transplantation day (efficacy analysis day 0). Further details on data handling conventions are specified in Section 7.10. For patients who took study drug but did not receive HCT, the analysis day will be calculated from the first study drug injection day (safety analysis day 1).

This SAP includes the plan for data analysis for the primary study period (i.e., 1-year post transplantation) which is defined as data collected through day 380 (=365+14+1 day) from transplantation. The long-term follow-up period is not covered by this SAP and will be managed in a separate SAP.

All data processing, summarization, and analyses will be performed using SAS® Version 9.4 or higher on Unix.

7.2 Study Population

7.2.1 Disposition of Subjects

Disposition of subjects will be summarized for the following:

- Number and percentage of subjects with informed consent, discontinued before randomization, and randomized (overall only);
- Number and percentage of subjects randomized in each analysis set, by treatment group and overall;
- 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 reason for study discontinuation for randomized subjects and by treatment group;
- Number and percentage of subjects excluded from the PPS by reason for exclusion defined in Section 5.3.1, by treatment group for the FAS and mFAS

Number of subjects randomized in each country and site will be tabulated by treatment group and overall.

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 the 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. Subjects who meet more than 1 criterion will be counted once in the overall summary. A data listing will be provided by site and subject.

The unique protocol deviation criterion 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 Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized descriptively by the treatment group and overall for FAS, mFAS, PPS-FAS, PPS-mFAS, SAF, mSAF, and xSAF populations.

Descriptive statistics for age, weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (Age < 65 years, Age ≥ 65 years), race, BMI categories (<25, 25 to <30, and ≥30 kg/m^2), ATG use, AML use, and myeloablative conditioning regimen will be done. Randomization strata donor-recipient

relatedness and donor CMV serostatus will be tabulated. Each of these combinations will also be tabulated. The ATG use (Yes/NO) and myeloablative or nonmyeloablative conditioning regimen will be tabulated from the eCRF according to the investigator's assessment.

Medical history is coded in MedDRA and will be summarized for treatment group and overall for SAF. One summary table will include SOC and PT and the other summary table will include PT in descending order of total group.

7.2.4 Previous and Concomitant Medications

Previous and concomitant medications are coded with WHO-DRL, 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 FAS and mFAS populations.

Previous medications are defined as medications that patients started and ended prior to first administration of study medication. Concomitant medications are defined as any medications that patients took after the first dose of study medication and through 1-year post-transplantation (i.e., 380 days from transplantation). Any previous medications that continued while study drug was given will be counted as both previous and concomitant medications.

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.

Antiviral therapies, including those used for reasons other than CMV infection, are of special interest. These medications will be summarized by reason for use.

7.2.5 Transplant Information

The following characteristics of the transplant procedure will be summarized by treatment group and overall for FAS and mFAS populations

- Recipient and donor HLA cross match at time of transplant
- Donor and recipient ABO and Rh blood types and cross match
- Number of CD34+ stem cells/kg infused
- Donor/recipient CMV serostatus
- Hepatitis B virus, Hepatitis C virus, and Epstein-Barr Virus serostatus of the donor and recipient, if available
- Donor-recipient relatedness
- Modified HCT-CI total score assessed by the investigator
- Product infused (bone marrow or peripheral blood stem cells)
- Donor cell product CMV-specific T-cells (optional and requires informed consent from donor)

The number of HLA mismatches will be summarized overall and separately by type (A, B, and DR) as categorical data. For the overall number of HLA mismatches, the following categories will be used: 0, 1, 2, ≥3. The derivation of HLA mismatches is detailed in Appendix 1

7.3 Study Drug

For each treatment group, descriptive statistics of the number of doses of the drug subject received will be presented. Descriptive statistics of time from first dose to final dose of study drug will be presented by treatment group. Furthermore, the number of subjects receiving study drug at each scheduled dose will be presented. These summaries will be produced for the FAS, mFAS, PPS-FAS, PPS-mFAS, SAF, mSAF, and xSAF populations.

All injections of study medication are to be administered when the subject's platelet count is ≥ 50000 mm^3 (spontaneously or after platelet transfusion) within 3 days prior to dosing. The numbers of subjects not receiving study drug injections due to this pre-condition will be summarized by treatment group. Additionally, the number of subjects who did receive injection although the subject's platelet count is <50,000 mm^3 will be tabulated.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis of the Primary Endpoint

The primary endpoint which is the composite of all-cause mortality and adjudicated CMV EOD through 1 year post-transplant will be analyzed for the FAS population as the primary analysis. Deaths occurring up to day 365 from transplant will be counted. In other words deaths occurring on or before 365 days after transplant will be counted, although it could be reported later. Patients with CMV EOD that is assessed by the independent and blinded adjudication committee will be counted for the events that are observed up to day 380 from transplantation.

The odds ratio of the composite endpoint for the ASP0113 group over the placebo group will be compared to unity controlling for randomization stratifications of donor-recipient relatedness and donor CMV serostatus by the Cochran-Mantel-Haenszel (CMH) test. The null (H0) and alternative hypotheses (H1) for this comparison are:

H0: Common Odds Ratio = 1.

H1: Common Odds Ratio ≠ 1.

The 2-sided p-values and the 95% confidence interval (CI) for the odds ratio from the CMH method will be calculated. The effect of ASP0113 will be considered statistically significantly superior to placebo if the p-value is less than 0.05.

Additionally, 1-RR with its 95% CI from the CMH method will be calculated as an additional descriptive summary.

For the purpose of the primary analysis, a subject who had a CMV EOD according to the adjudication committee and died will be counted in the mortality summary. A subject who died but the CMV EOD status is unknown will be counted toward the mortality summary. A subject with unknown survival status by day 365 will be counted a death if the subject does not have an adjudicated CMV EOD. A subject who is alive through day 365 and does not have the adjudicated CMV EOD will be counted as having no CMV EOD.

This derivation plan is also shown in the following table:

Composite Endpoint Derivation	Adjudicated CMV EOD is Yes	Adjudicated CMV EOD is not Yes
Survival Status=Died	Composite Endpoint=Yes (Count as Known Deaths)	Composite Endpoint=Yes (Count as Known Deaths)
Survival Status=Alive	Composite Endpoint=Yes (Count as Adjudicated CMV EOD)	Composite Endpoint=No
Survival Status=Unknown	Composite Endpoint=Yes (Count as Adjudicated CMV EOD)	Composite Endpoint=Yes (Count as Unknown Survival Status)

An additional analysis will be repeated for the mFAS, PPS-FAS and PPS-mFAS.

7.4.1.2 Additional Analyses of the Primary Efficacy Endpoint

Additionally, the primary efficacy endpoint will be further evaluated using a different method and different data source for the FAS and mFAS analysis sets.

Time to first occurrence of the primary endpoint event will be analyzed in a Cox proportional hazards model where the time to event will be calculated in days from transplant to the earliest component observed. Subjects not experiencing the primary endpoint event will be censored at the time of their last follow-up visit. The last day of follow up visit will be defined as last known day alive. If a subject's last known day alive is beyond day 380 and has no CMV EOD according to the adjudication committee, this subject will be censored on day 380. The Cox model will include treatment group, donor/recipient relatedness, donor serostatus (the stratification factors for randomization). Additionally, 1- hazard ratio and its 95% CI will be calculated.

Cumulative incidence functions (CIF) will be used to estimate the crude incidence of the primary endpoint by treatment group, and a Kaplan-Meier plot may also be considered.

7.4.1.3 Primary Analysis for Various Populations

As a supportive analysis for the primary efficacy endpoint of the composite endpoint of all-cause mortality and adjudicated CMV EOD through 1-year post-transplantation, the same CMH method as described in Section 7.4.1.1 will be further analyzed for the following analysis sets; mFAS, PPS-FAS and PPS-mFAS.

7.4.1.4 Subgroup Analysis

Subgroup analyses on the primary efficacy endpoint will be performed for FAS and mFAS analysis sets for the following subgroups:

- Donor-Recipient Relatedness: (Related, Not Related)
- Donor Serostatus: (Positive, Negative)
- Age group: (Age<65 years, Age ≥65 years)
- Sex: (Male, Female)
- Race: (White, Black or African American, Asian, Other)
- Geographic Region (North America, Europe, Asia, Australia)
- ATG Use for Conditioning: (ATG Used, No ATG Used)

- Myeloablative Conditioning Regimen: (Yes, No)
- AML Primary disease (Yes, No)

The observed odds ratio and its 95% CI based on the normal approximation for each level of subgroups will be calculated.

The treatment-by-subgroup interaction will be evaluated using a logistic regression model with factors for treatment group, donor-recipient relatedness, donor CMV serostatus, the subgroup of interest, and treatment-by-subgroup interaction. If a subgroup with a level that has fewer than 10 patients within any treatment group, the level will be excluded when the interaction is assessed. The interaction will be evaluated at the significance level of 0.10.

7.4.2 Analysis of Key and Other Secondary Efficacy Endpoints

Two of the secondary efficacy endpoints will be considered as key secondary efficacy endpoints.

7.4.2.1 Key Secondary Endpoint - Protocol-Defined CMV Viremia

The protocol-defined CMV viremia through 1 year post-transplant is defined as a CMV plasma viral load ≥1000 IU/mL by the central laboratory. The plasma viral load after transplantation through day 380 from transplantation day will be considered. A subject who has more than one time with CMV viral load ≥1000 IU/mL will be counted once. This endpoint will be analyzed by 2 statistical methods for FAS, mFAS and PPS-FAS.

A Cox proportional subdistributional hazards model will be used for the time-to-first protocol-defined CMV viremia through 1 year post-transplant. This model accounts for the competing risk of death, after which CMV Viremia can no longer be observed. A subject who has more than 1 incidence of having CMV viral load ≥1000 IU/mL will consider the first time of having this event. The Cox model will include treatment group, donor-recipient relatedness, donor CMV serostatus as factors in the model. From this model, 1 – Hazard Ratio and its 95% CI will be calculated. The p-value from this model will be calculated.

The treatment effect will also be evaluated with the following null hypothesis:

$$H_0: \text{1-Hazard Ratio} \leq 20\%.$$

While the alternative hypothesis is:

$$H_1: \text{1-Hazard Ratio} > 20\%.$$

The p-value for the above hypothesis tests will use a Wald statistic using the Cox model parameter estimate for the treatment effect, θ_t:

$$Z = (\theta_t - \ln(1\text{-}20\%))/\text{S.E.}(\theta_t)$$

CIFs will be used to estimate the crude incidence of CMV Viremia by treatment group while accounting for the competing risk of death.

The analysis window extends to day 380 from the transplantation day in order to accommodate the protocol allowed visit windows. If a subject's first event is after day 380, this subject will be censored on day 380 as the 1-year post transplantation is the primary

study period. A subject without an event will be censored on the last day of central laboratory assessment. In other words, if a subject has a central laboratory assessment beyond day 380 that is negative, this subject will be censored on day 380. A subject who dies prior to reporting CMV Viremia will be handled using a competing risks model.

Additionally, the same CMH method as in the primary endpoint will be used to calculate odds ratio and its 95% CI and 1-relative risk and its 95% CI. The p-value from this method will also be calculated.

7.4.2.2 Key Secondary Endpoint of Adjudicated CMV-Specific Antiviral Therapy

Subjects' CMV-specific antiviral therapy (AVT) use will be adjudicated by the independent and blinded committee. This endpoint will be evaluated through 1 year post-transplant (i.e., through day 380 from transplantation) and will be considered as a key secondary efficacy endpoint. This endpoint will be analyzed by 2 statistical methods for FAS, mFAS and PPS-FAS.

A Cox proportional subdistributional hazards model will be used for time-to-first use of CMV-specific AVT through 1 year post-transplant. This model accounts for the competing risk of death, after which use of CMV-specific AVT can no longer be observed. If a subject used CMV-specific AVT more than once, the day of first use will be counted. If a subject did not use any CMV-specific AVT, the subject will be censored on the day of last study evaluation according to the end of study eCRF.

To evaluate the treatment effect compared to placebo, 1-Hazard Ratio, its 95% CI and p-value from the Cox model (as in Section 7.4.2.1) will be calculated.

CIFs will be used to estimate the crude incidence of CMV-specific AVT while accounting for the competing risk of death.

Additionally, the same CMH method as in the primary endpoint will be used to calculate odds ratio and its 95% CI and 1-relative risk and its 95% CI. The p-value from this method will also be calculated.

7.4.2.3 Other Secondary Endpoints

7.4.2.3.1 CMV viremia and CMV-specific AVT Use

A composite endpoint of CMV viremia and CMV-specific AVT use per the adjudication committee will be analyzed as an additional secondary efficacy endpoint for FAS and mFAS analysis sets. The CMV viremia will be based on the protocol defined definition with plasma viral load ≥1000 IU/mL assessed by the central laboratory. Data that is observed through day 380 from transplantation will be included.

This endpoint will be analyzed using the same CMH method as in the primary endpoint.

7.4.2.3.2 Time to CMV-specific Antiviral Therapy or End Organ Disease

A composite endpoint of time to first event between CMV-specific Antiviral Therapy (AVT) use and CMV End Organ Disease (EOD) through 1 year post-transplant (i.e., through day 380 from transplantation) will be analyzed for FAS and mFAS. Both CMV-specific AVT use

and CMV EOD will be based on the assessment of the adjudication committee. A subject without any event will be censored on the last study evaluation according to the end of study eCRF. A subject who dies prior to reporting CMV-specific AVT or EOD will be handled using a competing risks model.

This endpoint will be analyzed using the Cox proportional subdistributional hazards model and CIFs (to account for the competing risk of death) and CMH method, as described above for the key secondary endpoints.

7.4.2.3.3 All-Cause Mortality

All-cause mortality will be analyzed by incidence and/or time to event approach for FAS and mFAS by treatment group.

All-cause mortality through 1-year post-transplantation summary will include all deaths and unknown survival status. For the known deaths, the adjudication committee assessed results will be summarized for the following category: Mortality due to the subject's primary disease, and Mortality due to causes unrelated to the subject's primary disease.

All-cause mortality will be analyzed by 2 methods: time to event and the CMH method, as described for the primary analysis. For the time to event analysis, a subject with unknown survival status will be censored on the last day known alive. For the CMH analysis, subjects with unknown survival status by day 365 will be counted as dead.

7.4.3 Exploratory Endpoints

The analyses of all exploratory endpoints will be performed on the FAS and mFAS analysis sets. All endpoints derived from subjects' visits will take an analysis window through day 380 from transplantation day while the mortality will be counted up to day 365.

7.4.3.1 Analyses of Clinical Outcomes Exploratory Endpoints

The following exploratory endpoints will be analyzed by incidence and/or time to event approach by treatment group.

For the endpoint of adjudicated CMV EOD, and Investigator-reported CMV EOD, the summary will include incidence (i.e., number of episodes) where all events are added in addition to the number and percentage of subjects with at least one event. The proportion of subjects with an event will be analyzed by the CMH method and the odds ratio, its 95% CI and p-value will be calculated.

- Composite endpoint of all-cause mortality and adjudicated CMV EOD at 6 months post-transplant, using the same CMH approach as the primary endpoint. Deaths occurring up to day 180 from transplant will be counted. In other words deaths occurring on or before 180 days after transplant will be counted, although the death could be reported later. Patients with CMV EOD that is assessed by the independent and blinded adjudication committee will be counted for the events that are observed up to day 190 from transplantation.

- All-cause mortality at 6 months post-transplant using time to event method, as described in Section 7.4.1.2. Deaths occurring up to day 180 from transplant will be counted. In other words deaths occurring on or before 180 days after transplant will be counted, although the death could be reported later.
- Relapse mortality (death due to relapse of the subject's primary disease), using the same CMH approach as the primary endpoint.
- Non-relapse mortality (death due to causes unrelated to the subject's primary disease), using the same CMH approach as the primary endpoint.

The proportion and number of subjects the events below will be descriptively summarized.

- Proportion of grade 3-4 aGVHD
- Proportion of engraftment (Yes/No)
- Proportion of graft rejection/poor graft function
- Proportion of relapse of primary disease requiring therapy

Additionally, number (percentage) of subjects by taking the maximum grade of aGVHD will be summarized.

Karnofsky Performance Scale (KPS) scores are collected at baseline and post-baseline. KPS scores will be descriptively summarized at baseline and the visits specified in schedule of assessments (Table 1), but KPS scores at any additional visits will only be listed.

The endpoint of grade 3 infections other than CMV will be summarized by the incidence counting all the events and number (percentage) of subjects. The number of subjects will be analyzed by the CMH method and the odds ratio, its 95% CI and the p-value will be calculated.

7.4.3.1.1 Association of CMV Viremia and Mortality

To estimate the association between CMV viremia and mortality, subjects in each treatment group will be cross-tabulated by viremia or no viremia within 1 year post-transplant, and by alive or dead at 1 year post-transplant. In addition, a multivariable Cox proportional hazards model will be constructed in a time-dependent manner. The model will be adjusted for the factors used to stratify the randomization. CMV viremia will be treated as a time-dependent variable, starting at the time of the first occurrence of protocol-defined CMV viremia. The model for this analysis will include, in addition to CMV viremia, all the factors included in the final Cox regression model described earlier in this subsection.

7.4.3.1.2 Number of Episodes of Protocol-defined CMV Viremia

Number of episodes of protocol-defined CMV viremia [CMV plasma viral load ≥1000 IU/mL by the Abbott RealTi*m*e CMV assay as assessed by the central laboratory] will be compared between treatments using the stratum-adjusted Kruskal-Wallis test, adjusting for donor-recipient relatedness and donor CMV status.

Number of episodes of protocol-defined CMV viremia may be affected by duration of follow-up. Therefore, as a supporting analysis this variable will be compared between

treatments using a log-linear model with treatment, donor-recipient relatedness, and donor serostatus as factors and the log of time of follow-up as a covariate.

7.4.3.2 Duration of Hospitalization, Health Economic, and Quality of Life Variables

Duration of hospitalizations, and days in emergency room, in days per year will be compared between treatments using descriptive statistics.

The number of emergency room visits, and Non-protocol-related physician visits, also will be compared between treatments using descriptive statistics.

The EQ-5D dimensions will be summarized as categorical variables by treatment arm at each visit and at final visit. Change from baseline in the EQ-5D VAS score will be summarized by treatment arm at each visit and at Final visit.

Total FACT-BMT and the corresponding changes from baseline will be summarized by treatment arm at each visit and at Final Visit.

The percent activity impairment due to health from the WPAI: GH and corresponding changes from baseline will be summarized by treatment arm at each visit and at Final Visit.

Treatments will be compared with respect to each of these scales using analysis of covariance (ANCOVA) of change from baseline to final visit with treatment, donor-recipient relatedness, and donor CMV serostatus as factors and baseline value as a covariate.

7.4.3.3 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 explanatory 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 unless specified otherwise.

The safety data will be summarized relative to the date of the first study drug injection through day 380 from the transplantation day. The safety data that was measured through day 380 will be included. This analysis window will accommodate the protocol visit windows.

7.5.1 Adverse Events

The coding dictionary for this study will be MedDRA. Treatment-emergent adverse event will be defined as an adverse event observed on the day or after the first injection up to 1 year post-transplant. If the adverse event occurs on the day of the first injection of study drug and the investigator marks as "Onset after first dose of study drug" or the onset check box is left blank in eCRF, then the adverse event will be considered treatment emergent. An overview table will include the following for the SAF, mSAF and xSAF :

- Number and percentage of subjects with at least one 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 death,
- Number and percentage of subjects with drug related TEAEs leading to death,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with related TEAEs leading to permanent discontinuation of study drug, and
- Number of deaths (on or before transplant Day 365 and after Day 365).

The number and percentage of subjects with TEAEs will be summarized for each treatment group. Summaries will be provided for:

- TEAEs by SOC, HLT and PT (for SAF, mSAF and xSAF populations)
- TEAEs by SOC, PT and CTCAE Grade
- TEAEs by severity (mild, moderate and severe)
- TEAEs by relationship to study drug assessed by investigator (Unlikely, possible and probable)
- serious TEAEs assessed by investigator and including Astellas always SAE,
- study drug related (possible and probable) TEAEs assessed by investigator
- study drug related (possible and probable) serious TEAEs by investigator and including Astellas always SAE
- TEAEs leading to permanent discontinuation of study drug,
- study drug related (possible and probable) TEAEs leading to permanent discontinuation of study drug
- TEAEs by PT in descending order of overall will be summarized
- TEAEs, PTs that equal or exceed a threshold of 5.0% in any treatment group, after excluding serious adverse events.

For the same event, a subject reports different severity, the worst severity will be counted. For the same event, a subject reports different study drug relationship, the highest degree of relationship will be counted.

Adverse Events of Interest

Adverse events of interest are as follows.

- Systemic reactions assessed by the sponsor medical review
- Late onset reactions assessed by the sponsor medical review
- Allergic and demyelinating reactions, to be identified using MedDRA SMQs for demyelination and anaphylactic.
- Local reactogenicity: AEs that are deemed by the Investigator as being associated with a local reactogenicity events. These are identified by a check box in the AE eCRF.
- Acute local vaccine reactions, including injection site Pain, Tenderness, Erythema/Redness, and Induration/Swelling are assessed by the Investigator for 60 minutes after each injection. For each subject, the reported grade on each scale following each injection, and overall the worst grade for each scale reported during the study will be summarized.

7.5.2 Local Reactogenicity Assessed by Subject

Local (non-acute) vaccine reactions, including injection site Pain, Tenderness, Redness, and Swelling or Hardening are assessed by the subject for each of the 7 consecutive days following each injection beginning approximately 24 hours after the dose (day 1-7 post dose). Local reactogenicity assessments will be summarized by treatment. For each subject, the worst reported grade on each scale observed following each injection and overall during the study will be summarized by treatment.

7.5.3 Clinical Laboratory Evaluation

Clinical laboratory data from central will be summarized by treatment group for SAF and mSAF. The baseline value for clinical laboratory evaluations is the last non-missing measurement taken prior to, or on the same day as, the initial injection of study drug.

Quantitative measurements from hematology and biochemistry will be summarized descriptively (n, mean, standard deviation, minimum, maximum and median for each treatment group at each visit). Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized.

Each laboratory result from central laboratory will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. The number and percentage of subjects below and above reference range will be summarized for each treatment group at each visit. Additionally, for medically important parameters, shifts from baseline to post-baseline in either the Low or High direction, and at Final Visit, will be summarized. The post-baseline category will be determined by taking the lowest or highest category for a subject, depending on direction of worsening. The Final Visit will be the last value of a subject within the analysis period.

7.5.3.1 Liver function tests

The liver function test parameters from central laboratory will assessed by the categories listed below. The number and percentage of subjects who meet the following criteria at post-baseline will be summarized.

- 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

Any subjects who have at least one post-baseline value will be included in this summary. A subject may be counted more than once as the categories are not mutually exclusive (i.e., a subject with a value >10xULN will be counted also in the subsequent categories). The last 3 criteria will be evaluated using the ALT and/or AST assessments that are conducted within 3 days of the Total Bilirubin and ALP assessments, as applicable.

7.5.4 Vital Signs

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

Vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, temperature and weight] will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-subject change will be calculated per visit and scheduled time as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit.

7.5.5 Pregnancies

A detailed listing of all pregnancies will be provided.

7.6 Analysis of PK

Not applicable.

7.7 Analysis of PD

Not applicable.

7.8 Safety Subgroups of Interest

The treatment emergent adverse events will be summarized by the treatment group for the subgroups defined based on the categorized variables listed below:

Grouping variable	Subgroups
Donor/Recipient Relatedness	Related Not Related
Donor CMV Serostatus	Positive Negative
Age group	Age < 65 years Age ≥ 65 years
Sex	Female Male
Race	White Black or African American Asian Other
Geographic Region	North America Europe Asia Australia

7.9 Interim Analysis and Early Discontinuation of the Clinical Study

Futility analyses will be conducted while the study is blinded by an independent data analysis center (DAC). Sponsor personnel will not have access to unblinded interim analysis data during the study unless the futility criterion is met and the sponsor needs to make a decision on discontinuing the trial.

7.9.1 Data Monitoring Committee

A DMC, independent of the Sponsor and Investigators, will be established to review the safety data throughout the study and to assess the futility of the study (See Section 7.9.2). The independent DMC statistician will have access to the randomization schedule. The DMC statistician and a separate independent data analysis center (DAC) will create or coordinate the unblinded deliverables for use by the DMC. The Sponsor will not have access to the unblinded tables and listings created for the DMC.

For details of the DMC refer to the DMC Charter.

7.9.2 Futility Analyses

Futility analyses were conducted according the pre-specified plans described in the DMC Charter. See DMC Charter for additional details.

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

7.10.1 Missing Data

For the primary efficacy endpoint, the various sensitivity analyses will be conducted in order to assess the impact of missing data as described in the sections above.

For the endpoints where the time to event approach is used, a subject without an event will be censored according to the description planned for each endpoint.

For all-cause mortality, subjects with unknown survival status by day 365 will be counted as dead in the crude summary.

The start and stop dates of AEs and concomitant medication will be imputed to determine whether a medication is prior and/or concomitant and to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the patient reported 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 the start date is missing or partial:

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

If the stop date is missing or partial:

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

If the imputed start date is after the stop date, then the imputed start date will be 1 day prior to the stop date.

For AEs, a missing or incomplete onset date will be imputed according to the following conventions.

If an onset date is missing or only the year is known, the imputed onset date will be the date of first dose of study drug.

If only the year is known for the AE onset date, the imputed onset date will be the latest of the following non-missing dates:

- Date of first dose of study drug
- January 1 of the year of AE onset date

If only the month and year is known for the onset date, set the surrogate onset date to the first day of that month and then apply the following rules.

- If the month and year of the onset date is prior to the month and year of the first dose of study drug, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date is on or after the month and year of the first dose of study drug, then the imputed onset date will be the **latest** of the following non-missing dates:
    - Date of first dose of study drug
    - Surrogate onset date

If the imputed onset date is after the adverse event end date, the imputed onset date will be the same as the adverse event end date.

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

7.10.2 Outliers

No outliers will be excluded from the analyses.

7.10.3 Visit Windows

All data collected up to 1-year post-transplant (i.e., day 380) will be included in the analysis, unless otherwise specified, except for mortality which is restricted to deaths occurring up to day 365 following the transplant. All data collected up to day 190 will be included in the 6-month post-transplant analyses, except for mortality which is restricted to deaths occurring up to day 180 following the transplant.

For efficacy analysis, data will be analyzed from the transplant day (day 0); for safety analysis, data will be analyzed from the first injection of study drug.

The summary by visits will follow the visits according to the CRF.

8 DOCUMENT REVISION HISTORY

8.1 List of Changes in SAP Version 3.0 from Version 2

The changes from the approved SAP Version 2 (Dated 15-Dec-2015) to Version 3.0 that impact analyses are listed with the rationale in the table below.

SAP Sections	Description	Rationale
5.1, 5.2, 7.4.1.1	FAS is considered to be the primary analysis population	Consistency with protocol, and adherence to intent-to-treat principles.
5.3.1	Removed several reasons for exclusion from PPS	Deleted reasons that appear to be confounded with, or have little direct impact on, primary endpoint.
6.1.2.2	All-cause mortality at 1 year post-transplant was elevated from exploratory to secondary endpoint.	All-cause mortality is a component of the primary efficacy endpoint.
6.1.2.2, 7.4.2.3	A composite endpoint of CMV viremia and CMV-specific AVT use per the adjudication committee has been added	To address suspicion of potential CMV-specific infection
6.1.3, 7.4.3.1	Added exploratory endpoints: all-cause mortality at 6 months, and composite endpoint of all-cause mortality and adjudicated CMV EOD at 6 months post-transplant.	In order to evaluate efficacy around the time of the last planned injection.
6.1.3	Removed a few exploratory endpoints: -Incidence of severe cGVHD -Maximum cGVHD -Incidence of failure to engraft -Time to engraftment -Time to platelet recover -Time to grade 3 treatment emergent viral, bacterial, or fungal infections other than CMV	Limited clinical relevance
7.1	Clarification of '1-year post transplant' study period for death and non-death events.	Day 365 for mortality and Day 380 for visit-based assessments to allow for protocol-allowed visit window.
7.2.4	Previous and concomitant medication summaries switched from safety (e.g., SAF) to efficacy (e.g., FAS) populations.	Medications are summarized for potential confounding of efficacy results.
7.4.1.1, 7.4.1.2	Added 1-RR from CMH and 1-HR from Cox Model	Feedback from FDA

7.5	Safety overview and TEAE summary by SOC, HLT and PT for SAF, mSAF, xSAF	All safety assessment to be done for SAF and mSAF. Summary based on xSAF were limited to high-level summaries as the xSAF population includes a limited number of subjects.
7.5	Updated list of AE of Interest Removed: Malignancies, Sinusoidal Obstruction Syndrome Added: Systemic reactions, late onset reactions	Improve alignment with clinical objectives.

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

10 APPENDICES

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

The HLA antigens are located on the cell surface. The genes encoding the HLA antigens are on chromosome 6 and have co-dominant expression: both alleles of one gene locus result in a surface HLA antigen. HLA class I antigens consist of a heavy chain and a β2m unit and include the HLA-A, HLA-B and HLA-C antigens, while HLA class II antigens are constituted by two heavy chains and include the HLA-DR, HLA-DP and HLA-DQ antigens. All HLA genes (loci) are very polymorphic: each has various alleles (variants) that can be distinguished by DNA sequencing of gene DNA or by serological techniques for detection of the gene products (the HLA antigens on the cell surface): HLA typing.

The HLA types for HLA-A, HLA-B and HLA-DR are entered in the eCRF. Broad HLA types comprise of several fine specificities, the narrow types, but it is only the broad type codes (roughly equivalent to the serologically defined antigen or serotype (allotype)) that are entered into the eCRF.

Example:

Donor:	HLA A		HLA B		HLA DR	
	A11	A66	B5	-	DR5	DR6

Recipient:	HLA A		HLA B		HLA DR	
	A25	A32	B12	B5	DR5	DR7

Both codes for a locus will be considered identical (homozygote) if only one code is entered. In this case, the investigator will either enter the code twice or put a dash for the second entry (or leave the second entry blank). The order of the entries is unimportant. A mismatch between a donor and a recipient exists if the donor has an antigen which doesn't appear in the recipient.

Calculation of the number of HLA mismatches:

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.

Appendix 2: Signatures

Prepared by: _____ Date: _____

[redacted], MS
Date (DD Mmm YYYY)

Approved by: _____ Date: _____

[redacted], PhD
Date (DD Mmm YYYY)

Approved by: _____ Date: _____

[redacted], MD
Date (DD Mmm YYYY)

Approved by: _____ Date: _____

[redacted], MBA
Date (DD Mmm YYYY)