Official Protocol Title:	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Letermovir (LET) Prophylaxis When Extended From 100 Days to 200 Days Post-Transplant in Cytomegalovirus (CMV) Seropositive Recipients (R+) of an Allogeneic Hematopoietic Stem Cell Transplant (HSCT)
NCT number:	NCT03930615
Document Date:	10-Jan-2020

Title Page

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Protocol Title: A Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT)

Protocol Number: 040-02

Compound Number: MK-8228

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

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Regulatory Agency Identifying Number(s):

EudraCT	2018-001038-17
IND	104,706 (tablet); 118,361 (IV)

Approval Date: 10 January 2020

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	10-JAN-2020	The primary purpose of this protocol amendment is to limit enrollment of participants who have anti-thymocyte globulin as the only high-risk category for CMV reactivation to ≤20% of the total trial population. This is to ensure that the preponderance of evidence does not come from participants with anti-thymocyte globulin as the only high-risk category for late CMV reactivation.
Amendment 01	23-AUG-2019	The primary purpose of this protocol amendment is to add the requirement that the intravenous (IV) formulation of letermovir (LET) supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials. This requirement is being added to prevent the possible administration of product-related particulate matter. The presence of visible product-related particulate matter is an expected characteristic of new clinical supplies of IV formulation of LET. This requirement is being implemented to allow for the release of new clinical supplies of IV LET, and as a precaution, it must be applied regardless of whether the clinical site considers its current clinical supply to be impacted. In addition, the matching placebo to the IV formulation of LET must also be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter and using DEHP-free IV bags and infusion set materials, in order to maintain the blind for IV study medications.
Original Protocol (Version 00)	03-DEC-2018	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [02]

Overall Rationale for the Amendments:

The primary purpose of this protocol amendment is to limit enrollment of participants who have anti-thymocyte globulin as the only high-risk category for CMV reactivation to ≤20% of the total trial population. This is to ensure that the preponderance of evidence does not come from participants with anti-thymocyte globulin as the only high-risk category for late CMV reactivation.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Criterion #5 ("at high risk of CMV disease, defined as meeting one or more of the following criteria"); Subpart "f": Was: "receipt of anti-thymocyte globulin" Now: "receipt of anti-thymocyte globulin (Note: enrollment of participants whose ONLY high-risk factor is the use of anti-thymocyte globulin will be restricted to ≤20% of all enrolled participants)"	To ensure adequate representation of all other subgroups of participants that are at high risk of CMV infection.
	Subpart "e": Was: "having T-cell–depleted grafts" Now: "having ex-vivo T-cell–depleted grafts"	To clarify that this criterion should be restricted to participants with ex vivo T-cell depletion only.

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered	Footnote added to Table 1 (*Study Therapy – Oral [Tablet] Formulation*) and Table 2 (*Study Therapy – Intravenous Formulation*) within the column header for "IMP/NIMP": "The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed."	To align with updated template text, allowing for country differences with respect to definition/classification of IMP/NIMP.
8.2.1 CMV DNA PCR Testing	Language added requiring sites in Japan to conduct pp65 antigen testing locally at the CMV infection visit along with the confirmatory CMV-DNA PCR test sample being sent to the central laboratory.	Most sites in Japan use pp65 antigen testing to drive decisions to initiate PET. Section modified to specify that such sites are required to obtain a repeat pp65 antigen test locally immediately prior to initiating anti-CMV therapy.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Table of laboratory tests [Table 9] restructured to identify those tests that must be performed by the central laboratory from those that may be performed by the central or the local laboratory. Table renamed (from "Laboratory Assessments Performed by the Central Laboratory" to "Laboratory Assessments")	Modified for improved clarity.
Global	Minor grammatical, typographical, and syntactical modifications made for improved accuracy and clarity, and to ensure consistency of language across the protocol.	

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT)

Short Title: Extension of LET from Day 100 to Day 200 post-transplant for the prevention of CMV infection in HSCT participants

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with the objectives in the Objectives and Endpoints table.

In CMV seropositive recipients (R+) of an allogeneic HSCT who have received LET prophylaxis through Day 100 post-transplant and are at high risk for CMV infection and/or disease after ~100 days post-transplant:

Primary Objectives	Primary Endpoints
Objective: To evaluate the efficacy of letermovir (LET) versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant Hypothesis (H1): LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant	Clinically significant CMV infection (CS-CMVi, defined as initiation of pre-emptive therapy [PET] for documented CMV viremia and/or CMV end-organ disease)

Secondary Objectives	Secondary Endpoints
To evaluate the safety and tolerability of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant based on the proportion of participants with adverse events from Week 14 post-transplant through Week 28 post-transplant.	AEs Study drug discontinuations due to AEs
To evaluate the efficacy of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the following: - Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 and from Week 14 post-transplant through Week 48 post-transplant - Time to onset of clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant - Proportion of participants with pre-emptive therapy (PET) for CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant - Proportion of participants with all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant - Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	Clinically significant CMV infection Initiation of anti-CMV PET for documented CMV viremia All-cause mortality

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Prevention of clinically significant CMV infection in adult allogeneic HSCT recipient
Population	CMV seropositive recipients post-transplant who have received LET prophylaxis through Day 100 post-transplant and are at high risk for CMV infection and/or disease after ~100 days post-transplant
Study Type	Interventional
Intervention Model	Parallel A multi-site study
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Investigator Participant Care Provider Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 36 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 216 participants will be randomized/enrolled.

Intervention Groups and Duration:

Intervention Groups

Drug	Dose Strength	Dose Frequency	Route of Administration	Use
LET				
LET (for participants on CsA)	240 mg	Once daily	Oral [a] or IV [b c]	Experimental
LET (for participants not on CsA)	480 mg	Once daily	Oral [a] or IV [b c]	Experimental
PLACEBO				
Placebo for LET	Not Applicable	Once daily	Oral [a] or IV [b c]	Placebo comparator
Duration: Interventions will be given from post-transplant Week 14 to post-transplant Week 28				

LET = letermovir; CsA = Cyclosporin A; IV = intravenous

a: The number of placebo tablets will mimic the LET dosing scheme in an effort to maintain the blind (ie, 1 matching placebo tablet if on CsA to mimic one 240-mg tablet; 1 or 2 matching placebo tablets if not on CsA to mimic one 480-mg tablet or two 240-mg tablets, respectively).

b: LET IV formulation dosing volume is 250 mL and duration of infusion will be approximately 60 minutes. LET IV will be provided as a sterile liquid concentrate for dilution (20 mg/mL), one vial to be used for the 240-mg dose and two vials for the 480-mg dose. Locally supplied sterile IV dextrose or saline diluent will be used as the placebo to LET IV as prepared by the site unblinded pharmacist.

c: The IV formulation should be switched to oral study therapy (ie, at the next planned dose) as soon as participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves.

Total Number	2 intervention groups
Duration of Participation	Each participant will participate in the study for approximately 36 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 2 weeks, each participant will be receiving assigned intervention for approximately 14 weeks. After the end of treatment each participant will be followed for 20 weeks.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1.	

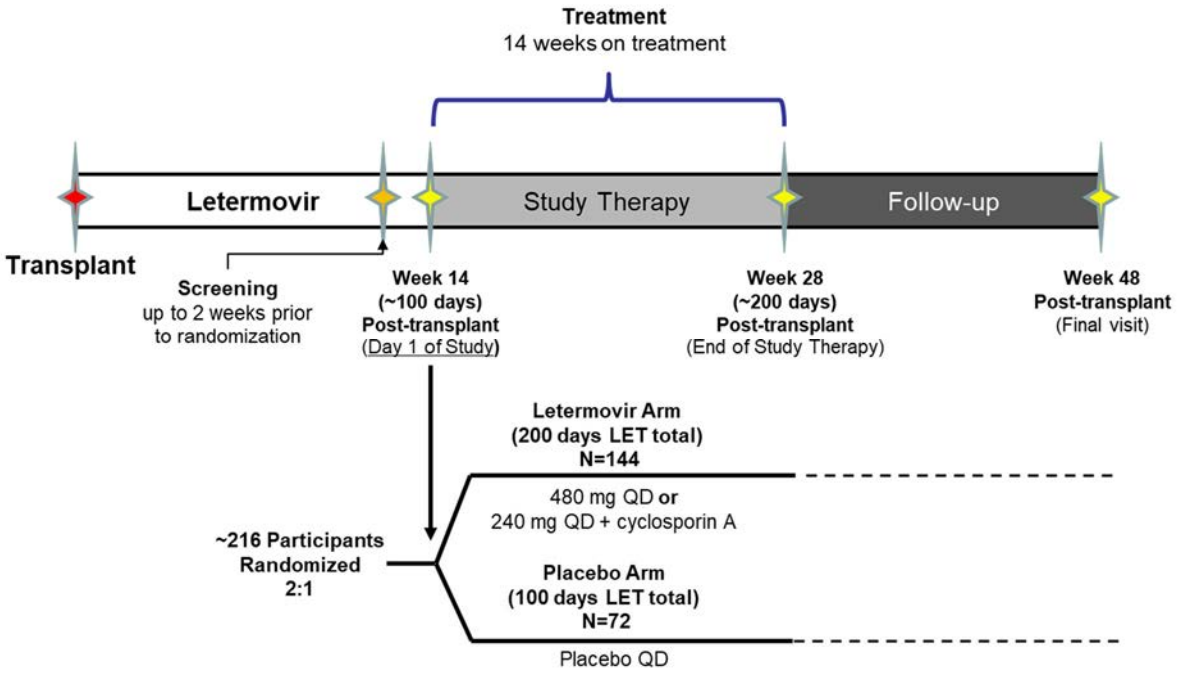
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



1.3 Schedule of Activities (SoA)

Study Period		**Treatment Period** (14 weeks of study therapy; Weeks 14-28 or ~100-200 days post-transplant)								**Follow-up**								CMVi or Early D/C [a, b]	Notes
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	D1 = Day 1 of study = day of randomization which should occur at 14 weeks (100 days) ±1 week post-transplant
Post-transplant Week	**SCR [c]**	**14 [d] (D1)**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32 [e]**	**34**	**36 [e]**	**38**	**40**	**44**	**48**		
Visit Window	-14 days		±3 days							±7 days						±14 days			
Administrative Procedures																			
Informed consent	×																		
Participant ID card	×																		Will be updated once randomized
Inclusion /exclusion	×	×																	
Medical history	×	×																	
Prior/conmeds review	×	×	×	×	×	×	×	×	×	×		×		×	×	×	×	×	
HSCT details review	×																		Collect conditioning regimen; date and type of transplant; source of stem cells; type of graft manipulation; presence of GVHD; and GVHD prophylaxis regimen (if any)
Treatment allocation		×																	
Study therapy dispensing		×	×	×	×	×	×	×											Contact IRT at all dispensing visits (See Section 8.1.8)
Study medication administration		×	×	×	×	×	×	×	×										

Study Period		**Treatment Period** (14 weeks of study therapy; Weeks 14-28 or ~100-200 days post-transplant)								**Follow-up**								CMVi or Early D/C [a, b]	Notes
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	D1 = Day 1 of study = day of randomization which should occur at 14 weeks (100 days) ±1 week post-transplant
Post-transplant Week	**SCR [c]**	**14 [d] (D1)**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32 [e]**	**34**	**36 [e]**	**38**	**40**	**44**	**48**		
Visit Window	-14 days		±3 days							±7 days						±14 days			
Study Medication Diary review		×	×	×	×	×	×	×	×										Participant will be trained on the use of Study Medication Diary on Day 1. Study Medication Diary will be collected/ redistributed at each visit after Day 1.
Clinical Procedures/ Assessments																			
Full Physical Examination	×	×																	
Targeted physical examination			×	×	×	×	×	×	×	×		×		×	×	×	×	×	Performed only when clinically indicated
Weight	×	×	×	×	×	×	×	×	×									×	
Height	×																		
Vital signs	×	×	×	×	×	×	×	×	×	×		×		×	×	×	×	×	HR, BP, respiratory rate, body temperature
12-lead ECG	×																		Read locally. Values collected within 1 month prior to screening may be used for Visit 1. Semi-recumbent position.
Child-Pugh score	×	×	×	×	×	×	×	×	×									×	Only when participant is on study medication. Laboratory testing for Child-Pugh scoring to be done locally after Visit 1
Confirm birth control (WOCBP only)	×	×	×	×	×	×	×	×	×	×		×						×	Acceptable methods of contraception to be used from the time of consent through 28 days after the last dose of study therapy.

Study Period		**Treatment Period** (14 weeks of study therapy; Weeks 14-28 or ~100-200 days post-transplant)								**Follow-up**								CMVi or Early D/C [a, b]	Notes
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	D1 = Day 1 of study = day of randomization which should occur at 14 weeks (100 days) ±1 week post-transplant
Post-transplant Week	**SCR [c]**	**14 [d] (D1)**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32 [e]**	**34**	**36 [e]**	**38**	**40**	**44**	**48**		
Visit Window	-14 days		±3 days							±7 days						±14 days			
AE monitoring	×	×	×	×	×	×	×	×	×	×		×		×	×	×	×	×	All AEs will be reported through 14 days after last dose of study medication. Thereafter, only drug-related SAEs or SAEs leading to death to reported until study completion (see Section 8.4)
Chemistry/ hematology	×	×	×	×	×	×	×	×	×	×								×	Refer to Section 8.3.4 for further details
Coagulation PT/INR	×	×	×	×	×	×	×	×	×									×	Performed centrally at Screening visit; locally thereafter
Urinalysis	×								×									×	Refer to Section 8.3.4 for further details regarding the laboratory safety tests
Serum (β-hCG) (WOCBP only)	×																		
Urine pregnancy (WOCBP only)		×		×		×		×										×	Performed locally; serum pregnancy test must be performed to confirm a positive urine test result.

Study Period		**Treatment Period** (14 weeks of study therapy; Weeks 14-28 or ~100-200 days post-transplant)								**Follow-up**								CMVi or Early D/C [a, b]	Notes
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	D1 = Day 1 of study = day of randomization which should occur at 14 weeks (100 days) ±1 week post-transplant
Post-transplant Week	**SCR [c]**	**14 [d] (D1)**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32 [e]**	**34**	**36 [e]**	**38**	**40**	**44**	**48**		
Visit Window	-14 days		±3 days							±7 days						±14 days			
HIV, Hepatitis B and C screen	×																		Documented neg HIV results at any time prior to screening acceptable. HBV/HCV to be done if not documented within the previous 6 months. If hepatitis C virus antibody is positive, RNA PCR results should be provided.
CMV Procedures/ Assessments																			
CMV DNA PCR	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
CMV disease assessment	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	All clinical signs and symptoms of CMV disease and review of relevant laboratory parameters
QuantiFERON-CMV assay	×								×								×	×	
CMV DNA sequence analysis																		× [f]	To be performed ONLY in participants with clinically significant CMV infection. Repeat samples should be collected at the next scheduled visit after the CMV Infection Visit.
Health Outcome Assessments		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	Collect re-hospitalizations, all-cause mortality, intravenous medications, select OIs, GVHD

β-hCG = β-Human Chorionic Gonadotropin; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; D = day; FU = follow-up; GVHD = graft-versus-host disease; HIV = human immunodeficiency virus; HSCT = hematopoietic stem cell transplant; IRT = interactive response technology; IV = intravenous; LET = letermovir; OI = opportunistic infection(s); PCR = polymerase chain reaction; PET = pre-emptive therapy; PT/INR = prothrombin time / international normalized ratio; SCR = screening; TP = Transplant; WOCBP = woman of childbearing potential.

a. This visit will be a **CMV Infection Visit** for all participants who meet the endpoint of CS-CMVi (defined as the occurrence of CMV disease or the initiation of PET) through Week 48 post-transplant. During the treatment period, LET must be discontinued at this visit (if the participant is still on LET). All procedures at the visit indicated in the SoA should be completed **immediately prior to** initiating PET for CMV infection or treatment for CMV disease at this visit (ie, on the day anti-CMV therapy is initiated). Most importantly, a plasma sample for CMV PCR testing at the central laboratory should be collected at this visit.
b. The visit will be an **Early Study Discontinuation Visit** for those participants who are prematurely discontinued from the study (not study medication alone) through Week 48 post-transplant.
c. Screening should begin after obtaining documented consent and must begin up to 14 days prior to the planned randomization date. The day of randomization (Day 1) will be approximately 14 weeks (100 days) ±1 week post-transplant. Participants will have plasma samples tested for CMV viremia using the CMV DNA PCR assay by the central laboratory.
d. Day 1 of the study is the day of randomization, and will occur 14 weeks (100 days) ±1 week post-transplant. On Day 1, eligibility for enrollment into the study will be confirmed. At that time, participants should have no documented quantifiable CMV viremia, as confirmed by CMV DNA PCR assay at the central laboratory in a plasma sample collected within 14 days prior to randomization. Creatinine clearance and liver function test results should also be available within 14 days prior to randomization. It is required that eligible participants have no more than 14 days of LET interruption prior to randomization.
Study therapy must begin on Day 1. Day 1 procedures/assessments must be performed prior to the first dose of study therapy.
e. A visiting nurse service may be utilized (if locally available and approved for use) for these visits in coordination with an investigator CMV assessment by phone. If a visiting nurse service is utilized, the investigator phone call should occur on the same day as the nurse visit, or as soon as possible. Refer to the nursing manual for additional details.
f. For participants with clinically significant CMV infection, a sample for CMV DNA sequence analysis for LET resistance should be collected at the CMVi visit **and** a second, confirmatory sample should be collected at the next scheduled visit following the CMVi visit.

2 INTRODUCTION

2.1 Study Rationale

Individuals who receive stem-cell or organ transplantation undergo immunosuppressive treatments that put them at high risk for select opportunistic infections. Cytomegalovirus (CMV) is the most common clinically significant viral infection after transplant, causing substantial morbidity and mortality in transplant recipients due to direct (eg, pneumonia, hepatitis, retinitis, encephalitis) [Boeckh, M. and Geballe, A. P. 2011] [Ljungman, P., et al 2002] [Boeckh, M. 2011], and indirect (eg, increased risk of select opportunistic bacterial and invasive fungal infections, graft-versus-host disease [GVHD], delayed engraftment or graft failure/rejection, increased overall mortality) effects [Craddock, C., et al 2001] [Miller, W., et al 1986] [Özdemir, E., et al 2007] [Martino, R., et al 2001] [Söderberg, C., et al 1993] [Larsson, K., et al 2004] [Marty, F. M. and Boeckh, M. 2011] [Ariza-Heredia, E. J., et al 2014]. Hematopoietic stem cell transplant (HSCT) recipients are at highest risk for CMV infection and/or disease within the first 100 days (approximately 14 weeks) after transplantation.

Letermovir (LET, also known as MK-8228, AIC246, AIC001) is a potent inhibitor of the CMV viral terminase and is approved for prophylaxis of CMV infection and/or disease in adult CMV seropositive recipients (R+) of an allogeneic HSCT. LET was overall well-tolerated and efficacious in a pivotal Phase 3 study (P001) for the prophylaxis of CMV infection or disease in adult CMV recipients R+ of an allogeneic HSCT [Marty, F. M., et al 2017]. In this randomized, placebo-controlled Phase 3 study, LET prophylaxis when started within 28 days post-transplant and continued until Week 14 (~100 days) post-transplant effectively prevented clinically significant CMV viremia through Week 24 post-transplant. At Week 14 post-transplant (end of study treatment), 19.1% participants on LET developed clinically significant CMV infection compared to 50% participants on placebo (non-completer=failure analysis, NC=F). After stopping LET at Week 14 post-transplant, there was an increase in clinically significant CMV infection through Week 24 post-transplant with 37.5% of participants on LET developing clinically significant CMV infection compared to 60.6% participants on placebo (p<0.0001) at Week 24 post-transplant (NC=F). The all-cause mortality at Weeks 24 and 48 after transplantation was lower in the LET group (10.2% and 20.9%, respectively) than the placebo group (15.9% and 25.5%, respectively). LET was well-tolerated with no evidence of myelotoxicity; participants who received LET had a similar time to engraftment (defined as the process of transplanted stem cells reproducing new cells) compared to those who received placebo.

The risk for CMV infection in HSCT recipients is reduced after the first 100 days post-transplant as the immune system reconstitutes. However, there are certain HSCT populations who remain at high risk for CMV infection beyond 100 days post-transplant due to delayed immune reconstitution, ongoing immunosuppression as a result of treatment for GVHD, or onset of new GVHD when immunosuppression is tapered. In a post-hoc analysis of results from P001, factors predictive of the development of clinically significant CMV infection between Weeks 14 and 24 post-transplant include high risk stratum at baseline (based on donor relatedness and degree of matching, stem-cell source, and T-cell depleted

grafts), occurrence of GVHD, and steroid use following randomization. CMV infection occurring after ~100 days post-transplant is associated with morbidity and is an independent predictor of mortality [Erard, V, Guthrie, K. A. 2015]. However, the benefit of prolonged prophylaxis for prevention of CMV infection/disease after 100 days post-transplant in HSCT recipients remains unclear. The standard of care for prevention of CMV infection/disease after 100 days post-transplant remains pre-emptive therapy (PET), which is defined as the practice of active surveillance for viral replication with antiviral treatment started only when CMV viremia is detected [Ljungman, P., et al 2002]. In a randomized, double-blind trial of CMV prophylaxis with valganciclovir (VGCV) compared to placebo/PET between ~3-6 months post-HSCT, CMV viremia was reduced in the VGCV group compared to placebo (11% vs 36% respectively, $p<0.001$), but there was no difference in survival between the two arms [Boeckh, M., et al 2015].

The objective of this study is to evaluate the occurrence of clinically significant CMV infection when LET prophylaxis is extended from Day 100 to Day 200 post-transplant in CMV R+ recipients of an allogeneic HSCT who have received LET prophylaxis through Day 100 post-transplant and are at high risk for CMV infection and/or disease after ~100 days post-transplant. The data from this study may guide the clinical management of CMV in allogeneic HSCT recipients who continue to be at high risk of CMV infection after ~100 days post-transplant.

2.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on LET.

2.2.1 Pharmaceutical and Therapeutic Background

LET is a novel inhibitor of the CMV viral enzyme DNA terminase (UL56/UL89/UL51), an enzyme that plays an important role in the cleavage of newly synthesized concatenated CMV DNA into individual unit-length viral genomes that are subsequently inserted into CMV procapsids to generate infectious CMV virions [Goldner, T., et al 2011]. LET has demonstrated potent, selective, and reversible inhibition of CMV activity in preclinical studies in vitro and efficacy against the virus in vivo [Lischka, P., et al 2010] [Goldner, T., et al 2011].

LET is currently available commercially as oral tablet formulations and an intravenous formulation. Participants in this study will either receive the currently marketed oral adult tablets (240-mg or 480-mg strength) or marketed intravenous formulation or placebo.

2.2.2 Preclinical and Completed Clinical Studies

Details of preclinical studies and completed clinical studies conducted with LET can be found in the accompanying IB.

2.2.3 Ongoing Clinical Studies

One clinical study (P002) with LET is currently ongoing. It is a Phase 3 randomized, multi-site, double-blind active comparator trial to evaluate the efficacy and safety of LET versus VGCV in adult kidney transplant recipients. Adult CMV donor seropositive (D+)/recipient seronegative (R-) kidney transplant recipients are being enrolled to receive either LET or VCVG starting within 7 days post-transplant and continuing through Week 28 post-transplant. Efficacy will be measured by the proportion of participants with adjudicated CMV disease through Week 52 post-transplant. Safety and tolerability in kidney transplant recipients will also be evaluated.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with the objectives in the Objectives and Endpoints table.

In CMV seropositive recipients (R+) of an allogeneic HSCT who have received LET prophylaxis through Day 100 post-transplant and are at high risk for CMV infection and/or disease after ~100 days post-transplant:

Objectives	Endpoints
Primary	
• Objective: To evaluate the efficacy of letermovir (LET) versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant • Hypothesis (H1): LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant	• Clinically significant CMV infection (CS-CMVi, defined as initiation of pre-emptive therapy [PET] for documented CMV viremia and/or CMV end-organ disease)

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant based on the proportion of participants with adverse events from Week 14 post-transplant through Week 28 post-transplant.	• AEs • Study drug discontinuations due to AEs
• To evaluate the efficacy of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the following: • Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 and from Week 14 post-transplant through Week 48 post-transplant • Time to onset of clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant • Proportion of participants with pre-emptive therapy (PET) for CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant • Proportion of participants with all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	• Clinically significant CMV infection • Initiation of anti-CMV PET for documented CMV viremia • All-cause mortality

Objectives	Endpoints
• Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	
Exploratory	
• To evaluate the efficacy of LET versus placebo when LET prophylaxis is extended from 100 to 200 days post-transplant, as measured by the following: • Proportion of participants with CMV end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant • Proportion of participants with documented CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	• CMV end-organ disease • Documented CMV viremia ≥300 copies/mL
• To evaluate health outcomes in LET versus placebo from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	• Recurrent episodes of CMV infection • Select opportunistic infections other than CMV infection • Graft-versus-host disease (GVHD) • All re-hospitalizations and re-hospitalizations for CMV infection/disease • Intravenous medications other than LET

Objectives	Endpoints
• To evaluate the antiviral resistance to LET in subjects with clinically significant CMV infection from Week 14 post-transplant through Week 48 post-transplant.	• Antiviral resistance to LET in prophylaxis failures

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blinded, efficacy and safety study of extending LET prophylaxis in CMV R+ HSCT recipients who have already received LET prophylaxis through Week 14 (~100 days) post-transplant and who are at high risk for CMV infection and/or disease thereafter. This trial will enroll approximately 216 allogeneic CMV R+ HSCT recipients who have already received LET prophylaxis that started within 28 days after HSCT and continued through approximately 14 weeks post-transplant prior to randomization in this study. Eligible participants will be randomized in a 2:1 ratio to continue their LET treatment uninterrupted for an additional 14 weeks (~100 days of LET treatment for a total of 200 days of LET post-transplant) or to begin receiving placebo (a total of 100 days of LET post-transplant). LET will be administered as either 480 mg QD or 240 mg QD for those participants who are receiving concomitant cyclosporin A (CsA). The LET dose is reduced to 240 mg QD when coadministered with CsA based on an increase in LET exposures of approximately 2-fold in healthy volunteers (P010) and Phase 3 study (P001). Participants will receive 14 weeks of study treatment through Week 28 post-transplant and be followed to Week 48 post-transplant to evaluate post-prophylaxis CMV infection events.

In order to ensure safe study conduct, an independent external Data Monitoring Committee (DMC) will be established for safety evaluation. The DMC will review safety data at proposed time points outlined in Section 9.7 and as detailed in the DMC charter. The DMC will review safety data, consider the overall risk and benefit of continuing the study to study participants, and make a recommendation to the Sponsor to continue, modify, or end the study.

An independent blinded Clinical Adjudication Committee (CAC) will be established for this study to adjudicate all potential CMV disease cases as identified by site investigators or as otherwise described in the CAC charter.

Participants who discontinue study medication early (ie, prior to Week 28 post-transplant) are intended to complete all remaining treatment period visits through Week 28 post-transplant, as well as all remaining visits through Week 48 post-transplant as outlined in the Schedule of Activities (SoA). All scheduled study visits will be completed regardless of when cessation of study treatment occurs.

A visiting nurse service may be utilized (if locally available and approved for use) for the Weeks 32 and 36 post-transplant visits in the follow-up phase of the study. Refer to the nursing manual for additional details.

For participants who develop clinically significant CMV infection, the participant should have a **CMV Infection Visit**. It is very important to ensure that all procedures, as outlined in the SoA, are performed at the CMV Infection Visit **immediately prior to** the initiation of treatment for CMV disease or initiation of PET. Such participants will continue to be followed in the study (despite discontinuing study therapy, and if applicable, initiating anti-CMV therapy) and are intended to complete all remaining study visits (including all subsequent treatment period visits).

Participants who discontinue the study prior to Week 48 post-transplant should complete an Early Discontinuation Visit.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

Population

Overall, HSCT recipients who are CMV R+ have increased non-relapse mortality compared to CMV seronegative recipients [Teira, P., et al 2016]. Additional risk factors for developing clinically significant CMV infection beyond the first 100 days post-transplant that may require extended CMV prophylaxis therapy include HLA mismatch, T-cell depletion [Huang, Y. T., et al 2016] including the use of anti-thymocyte globulin, receipt of cord blood allograft [Boeckh, M. and Nichols, W. G. 2004] or allograft from haploidentical donor, and recipients who have GVHD requiring the use of high dose steroids. As such, CMV R+ HSCT recipients who have one or more of these high-risk factors for developing clinically significant CMV infection beyond 100 days post-transplant are selected for this study.

Randomization and Stratification

Study P001 demonstrated that LET prophylaxis during the first 14 weeks after HSCT is effective and well-tolerated in preventing clinically significant CMV infection. In the present study, CMV R+ HSCT recipients who have received LET prophylaxis through Week 14 post-transplant are randomized to receive either 14 weeks of LET or placebo until Week 28 post-transplant. The timing of randomization of participants at Week 14 (~Day 100) post-transplant is selected to reflect the time the clinical decision is made of whether to extend the duration of CMV prophylaxis. This study will randomize in a 2:1 ratio with a total of 216 participants with 144 in the LET (200-day) arm and 72 in the placebo (100-day) arm in order to allow more participants to potentially benefit from LET prophylaxis. Randomization will be stratified by study center in order to balance varying clinical practices of PET initiation and types of transplants at different centers. In addition,

randomization will also be stratified by participants who received cells from a haploidentical donor, as this represents a defined large population with a baseline risk factor for CMV infection. Note that it is possible that some sites will only enroll participants with the same haploidentical donor status (either all yes or all no). The number of participants who received cells from a haploidentical donor will be capped at ~30% of total participants.

Treatment Duration

A study in recipients of solid-organ transplants demonstrated that the incidence of CMV disease at 12 months post-transplant can be significantly reduced if 200 days of prophylaxis is implemented instead of 100 days [Humar, A., et al 2010]. Similarly, the prolongation of prophylaxis to Week 28 post-transplant could be a potential strategy to decrease the incidence of clinical significant CMV infection in certain HSCT recipients at high risk for CMV infection. As such, an additional 100 days of LET or placebo beyond the initial LET prophylaxis after 100 days post-transplant HSCT will be evaluated in HSCT recipients who are at high risk of CMV infection after 100 days post-transplant. The proportion of clinically significant CMV infection will be assessed at the end of study therapy at Week 28 post-transplant as the primary endpoint.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint of the study will be the proportion of participants with clinically significant CMV infection post-transplant, which is defined as the occurrence of either one of the following outcomes:

- onset of CMV end-organ disease (probable or proven)

  OR

- initiation of anti-CMV PET with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia and the clinical condition of the participant

The composite endpoint of clinically significant CMV infection used in study P001 was selected for this study because CMV infection (as measured by CMV viremia) is associated with increased morbidity and mortality in HSCT recipients. It is difficult to use CMV end-organ disease alone as the sole clinical endpoint due to low incidence of CMV disease in HSCT recipients as a result of PET. The results of P001 demonstrate that the composite endpoint of clinically significant CMV infection is a relevant clinical endpoint [Marty, F. M., et al 2017]. The primary endpoint will be assessed at the end of study therapy (Week 28 post-transplant). This endpoint will also be assessed at multiple time points post-transplant as secondary endpoints in order to describe the natural history of clinically significant CMV infection after an extended duration of LET prophylaxis.

In this study, CMV DNA PCR testing will be measured from plasma samples using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) assay, which will be performed by the central laboratory. The lower limit of quantification (LLoQ) for this assay is 137 IU/mL, which is approximately 151 copies/mL (using a conversion factor of 1.1 copies/IU as per the assay package insert). The CMV DNA levels in IU/mL will be reported as one of the following:

- <137 NOT DETECTED
- <137 DETECTED NOT QUANTIFIABLE
- A numeric value
- >910,000,000

In this study, any *quantifiable* CMV viral DNA result on a confirmatory sample obtained immediately prior to (ie, on the day of) the initiation of treatment for CMV disease or PET using central CMV PCR assay is acceptable for documenting viremia as a component of the efficacy endpoint. In addition to documented CMV viremia, the investigator should also take into account the clinical condition of the study participant when deciding to initiate PET. Quantifiable CMV viral DNA alone without initiation of anti-CMV therapy will not be considered as a case for clinically significant CMV infection in the primary efficacy analysis.

While any quantifiable CMV viral DNA results in the Roche CAP/CTM assay from confirmatory plasma sample sent to the central laboratory is acceptable for the purpose of documenting viremia as a component of the primary endpoint, it is recommended that investigators consider initiating PET when CMV DNA viral load is approximately >274 IU/mL or >300 copies/mL. This threshold for initiation of PET is provided as guidance and is not mandated since a participant's clinical condition and the need for PET is best assessed by the investigator.

All cases of potential CMV disease will be determined using the definitions in Appendix 7 (Section 10.7) and confirmed by an independent, blinded CAC. The CAC will review clinical, virological, and histopathological data as well as the investigator's assessment for adjudicating all potential cases of CMV disease. The adjudication of cases by the CAC will take precedence over the investigator's assessment for the purpose of analysis.

4.2.1.2 Safety Endpoints

The safety and tolerability of LET will be assessed by a clinical evaluation of adverse experiences and evaluation of other study parameters including vital signs, physical examination, and standard laboratory safety tests at appropriate time points.

4.2.1.3 Other Endpoints

CMV Immune Response

CMV-specific T-cell immunity is the predominant adaptive immune response that confers protection against CMV [Manuel, O., et al 2013] [Abate, D., et al 2013] [Cantisan, S., et al 2013] [Fernandez-Ruiz, M., et al 2014]. A delayed recovery of T-cell immunity post-transplant has been observed with long-term viral suppression [Reusser, P., et al 1991], which may potentially lead to continued risk of CMV infection. However, the association between antiviral prophylaxis and delayed immune reconstitutions is inconsistent [Zaia, J. A., et al 1997] [Boeckh, M., et al 2006]. Preclinical data suggest that treatment with LET is accompanied by the cytoplasmic accumulation of large amounts of subviral, noninfectious particles termed dense bodies (DBs) within CMV-infected cells [Goldner, T., et al 2011]. As DBs are immunogenic and are known to prime lymphocytes and neutralizing antibodies in mice, it is possible that the release of noninfectious, immunogenic DB during LET prophylaxis may facilitate the development of antiviral immune response following HSCT. In order to understand the impact that prolonged LET prophylaxis has on the development of CMV-specific T-cell responses in individuals who are at high risk of clinically significant CMV infection/disease beyond the initial 100 days post-transplant, the correlation between the proportion of participants who develop CMV-specific T-cell responses and clinically significant CMV infection in the LET and placebo groups will be assessed as an exploratory endpoint in this study. The proportion of participants with positive QuantiFERON-CMV assay results will be correlated with the incidence of clinically significant CMV infection through Week 48 post-transplant and assessed as an exploratory endpoint.

Health Outcomes Assessment

The occurrence and treatment of CMV infection is associated with significant resource utilization in the first 6 months post-transplant [Martin, P. J. 2008]. Use of intravenous medications serve as a proxy measure of patient medication burden, especially if they need to travel to a healthcare facility to receive the treatment. It is important to collect healthcare resource utilization data since an extended duration of prophylaxis will be accompanied by increases in the total cost of the prophylaxis regimen. Payers, public healthcare systems, insurance providers, clinicians, and other decision makers will require data on health-outcomes measures (such as incidence of all-cause mortality, rehospitalizations, GVHD, select opportunistic infections, intravenous medication use, and recurrent CMV infection) to inform analyses of budget impact and cost effectiveness. Clinical trials are important sources of health economic data as they have high internal validity and can produce unbiased estimates of economic benefits. As such, to evaluate if extended duration of LET prophylaxis is associated with changes in the utilization of healthcare resources, healthcare resource utilization data are collected for all participants throughout the study. The data collected may be used to conduct exploratory economic analyses.

4.2.2 Rationale for the Use of Comparator/Placebo

It has not yet been shown that there is clinical benefit to continuing CMV prophylaxis in HSCT recipients after 100 days post-transplant. Therefore, the efficacy and safety of LET with monitoring/PET will be compared against placebo and monitoring/PET, which is the standard of care for CMV management for allogeneic HSCT recipients who are at risk of CMV infection/disease after Day 100 post-transplant. The trial is designed to evaluate if LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant. The use of a placebo-controlled design will also allow a robust evaluation of the safety profile of LET beyond the initial 100 days post-transplant.

4.3 Justification for Dose

The doses of LET selected in this study are 480 mg QD orally or intravenously, or 240 mg QD orally or intravenously when coadministered with CsA. The LET dose is reduced to 240 mg QD when coadministered with CsA based on the observed increase in LET exposures in a Phase 1 DDI trial in healthy subjects (P010) and Phase 3 study (P001). These LET doses have been approved for prophylaxis of CMV in HSCT recipients. Since the oral formulation of LET demonstrates no clinically significant food effect, participants may take the study drug orally without regard to food. Refer to the IB for details on dose justification; the rationale for the doses selected is briefly summarized in this section.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

Early study termination will be the result of the criterion specified below:

- The DMC recommends termination of the study and the Executive Oversight Committee (EOC) agrees as stated in the DMC charter.

- The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable.

Details for the discontinuation of study medication for any given participant are provided in Section 7.1.

5 STUDY POPULATION

Male and female CMV R+ participants of at least 18 years of age who had an allogeneic HSCT and have received LET as primary CMV prophylaxis that started within 28 days of HSCT and continued through 14 weeks post-transplant will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. have documented positive CMV serostatus (CMV IgG seropositive) for recipient (R+) at the time of transplant.

2. history of allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant) within ~100 days prior to randomization.

3. have undetectable CMV DNA or detectable/not quantifiable CMV DNA (central laboratory) from a plasma sample collected within 14 days prior to randomization.

4. have received LET as primary prophylaxis that started within 28 days of HSCT and continued through Week 14 post-transplant (100 days) ±1 week prior to randomization.

5. at high risk of CMV disease, defined as meeting one or more of the following criteria:

    a. having a related donor with at least one mismatch at one of the specified three HLA gene loci (HLA-A, B, or DR);

    b. having an unrelated donor with at least one mismatch at one of the specified four HLA gene loci (HLA-A, B, C, and DRB1);

    c. having a haploidentical donor;

    d. having umbilical cord blood as the stem-cell source;

    e. having ex-vivo T-cell–depleted grafts;

    f. receipt of anti-thymocyte globulin (Note: enrollment of participants whose ONLY high-risk factor is the use of anti-thymocyte globulin will be restricted to ≤20% of all enrolled participants);

    g. receipt of alemtuzumab;

    h. having GVHD or other conditions, requiring the use of systemic prednisone (or equivalent) at a dose of ≥1 mg/kg of body weight per day within 6 weeks of randomization.

Demographics

6. Participant is ≥18 years of age at the time of signing the informed consent.

Female Participants

7. A female participant is eligible to participate if she is not pregnant (Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

      OR

   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 28 days after the last dose of study medication.

Informed Consent

8. The participant (or legally acceptable representative if applicable) provides written informed consent for the study.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. has a history of CMV end-organ disease or preemptive treatment therapy for CMV after HSCT prior to randomization.

2. has a history of >14 days total of LET interruption during the first 100 days post-transplant prior to randomization.

3. has suspected or known hypersensitivity to active or inactive ingredients of LET formulations.

4. has severe hepatic insufficiency defined as Child-Pugh Class C (see Appendix 8, Section 10.8) within 14 days prior to randomization.

5. has serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5× the upper limit of normal (ULN) within 14 days prior to randomization.

   Note: Participants who meet this exclusion criterion may, at the discretion of the investigator, have repeat testing done one time prior to randomization. If the repeat value does not meet this criterion, they may continue in the screening process. Only the specific out of range value should be repeated (not the entire panel).

6. has end-stage renal impairment with a creatinine clearance less than 10 mL/min, as calculated by the Cockcroft-Gault equation using serum creatinine within 14 days prior to randomization

   $$\text{Creatinine Clearance (Males)} = \frac{\text{weight in kg} \times (140 - \text{age in years})}{72 \times \text{serum creatinine in mg/dL}}$$

   Creatinine Clearance (Females) = 0.85× the value obtained with formula above

   Note: Participants who meet this exclusion criterion may, at the discretion of the investigator, have repeat testing done one time within 14 days prior to randomization. If the repeat value does not meet this criterion, they may continue in the screening process. Only the specific out of range value should be repeated (not the entire panel).

7. has both moderate hepatic insufficiency AND moderate-to-severe renal insufficiency.

   Note: Moderate hepatic insufficiency is defined as Child-Pugh Class B (see Appendix 8); moderate-to-severe renal insufficiency is defined as a creatinine clearance less than 50 mL/min, as calculated by the Cockcroft-Gault equation (as above), respectively.

8. has an uncontrolled infection on the day of enrollment.

9. requires mechanical ventilation or is hemodynamically unstable at the time of enrollment.

10. has a documented positive result for a human immunodeficiency virus antibody (HIV-Ab) test at any time prior to screening, or for hepatitis C virus antibody (HCV-Ab) with detectable HCV RNA, or hepatitis B surface antigen (HBsAg) within the 6 months prior to screening.

11. has active solid tumor malignancies (with the exception of localized basal cell or squamous cell skin cancer).

Prior/Concomitant Therapy

12. Received within 7 days prior to screening any of the following:

    - ganciclovir or valganciclovir
    - foscarnet
    - acyclovir (at doses greater than those recommended for HSV/VZV prophylaxis; see Sec. 6.5.2.1)
    - valacyclovir (at doses greater than those recommended for HSV/VZV prophylaxis; see Sec. 6.5.2.1)
    - famciclovir (at doses greater than those recommended for HSV/VZV prophylaxis; see Sec. 6.5.2.1)

13. Received within 30 days prior to screening any of the following:

    - cidofovir
    - CMV immunoglobulin

Prior/Concurrent Clinical Study Experience

14. is currently participating or has participated in a study with an *unapproved* investigational compound, monoclonal antibody, or device within 28 days or 5× half-life of the investigational compound or monoclonal antibody, whichever is longer, of initial dosing in this study.

    Note: Investigational chemotherapy regimens involving *approved* agents and investigational antimicrobial regimens involving *approved* antibacterial/antifungal/antiviral agents, investigational radiotherapy or GVHD agents, or other observational studies are allowed.

15. has previously participated in this study or any other study involving LET, or is currently participating in any study involving administration of a CMV vaccine or another CMV investigational agent, or is planning to participate in a study of a CMV vaccine or another CMV investigational agent during the course of this study.

Other Exclusions

16. is pregnant or expecting to conceive, is breastfeeding, or plans to breastfeed from the time of consent through 28 days after the last dose of study therapy.

17. is expecting to donate eggs starting from the time of consent through 28 days after the last dose of study therapy.

18. has clinically relevant drug or alcohol abuse within 12 months of screening that may interfere with participant treatment, assessment, or compliance with the protocol as assessed by the investigator.

19. has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or would be put at undue risk as judged by the investigator, such that it is not in the best interest of the participant to participate in this study.

20. is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

The oral formulation of LET demonstrates no clinically significant food effect, thus participants may take the study drug orally without regard to food. However, there may be restrictions with other nonstudy treatment agents the participant is taking during the study and therefore it is important for investigators to refer to the product information for those agents (ie, participants who are taking CsA concomitantly with LET must avoid consumption of grapefruit and grapefruit juice).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study medication or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies, study intervention(s) provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study medication(s) to be used in this study are outlined in Table 1 (oral formulation) and Table 2 (IV formulation). Both the 240-mg (for participants on CsA) and 480-mg (for participants not on CsA) oral formulations of LET will be made available by the Sponsor. Approximately 216 participants who have received LET through 100 days post-transplant are planned for randomization in a 2:1 ratio to receive either an additional 100 days (14 weeks) of once-daily LET (n=144 participants) or placebo (n=72 participants) from the day of enrollment (Day 1—ie, 100 days [14 weeks] post-transplant) through 28 weeks post-transplant. Participants on 480 mg will receive either one 480-mg tablet or two 240-mg tablets (based on the participants' tolerance to swallowing the larger 480-mg tablet). The IV formulation of LET will be available for participants randomized to LET who develop a condition that may interfere with their ability to swallow, or a condition that interferes with the absorption of the oral formulation (eg, vomiting, diarrhea, or a malabsorptive condition). Participants randomized to placebo who develop a condition that may interfere with their ability to swallow, or a condition that interferes with the absorption of the oral formulation will be able to receive IV administration of placebo. The simultaneous use of IV and oral study therapy is not permitted. Use of the IV formulation should generally be limited to a duration of 4 weeks or less; however, IV administration beyond 4 weeks will be permitted if, in the investigator's judgment, the benefit/risk supports continued administration. There is no sponsor-provided placebo for IV LET. On-site blinding will be administered by an unblinded pharmacist using open label IV LET (20 mg/mL, 12-mL fill vial) and locally supplied sterile IV dextrose or saline diluent as the placebo.

Table 1 Study Therapy – Oral (Tablet) Formulation

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP [a]	Sourcing
LET (for participants on CsA)	240 mg	Once daily	Oral	From Week 14 post-transplant to Week 28 post-transplant	Experimental	IMP	Sponsor
LET (for participants not on CsA)	480 mg (one 480-mg tablet or two 240-mg tablets)	Once daily	Oral	From Week 14 post-transplant to Week 28 post-transplant	Experimental	IMP	Sponsor
Placebo for LET [b]	NA	Once daily	Oral	From Week 14 post-transplant to Week 28 post-transplant	Placebo	IMP	Sponsor

CsA = Cyclosporin A; IMP = investigational medicinal product; LET = letermovir; NIMP = noninvestigational medicinal product

a: The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

b: The number of placebo tablets will mimic the LET dosing scheme in an effort to maintain the blind (ie, 1 matching placebo tablet if on CsA; 1 or 2 matching placebo tablets if not on CsA to mimic one 480-mg tablet or two 240-mg tablets, respectively).

Table 2 Study Therapy – Intravenous Formulation

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP [a]	Sourcing
LET (for participants on CsA) [b]	240 mg	Once daily	IV	From Week 14 post-transplant to Week 28 [c] post-transplant	Experimental	IMP	Sponsor
LET (for participants not on CsA) [b]	480 mg	Once daily	IV	From Week 14 post-transplant to Week 28 [c] post-transplant	Experimental	IMP	Sponsor
Placebo for LET [b]	NA	Once daily	IV	From Week 14 post-transplant to Week 28 [c] post-transplant	Placebo	IMP	Site locally

CsA = Cyclosporin A; IMP = investigational medicinal product; LET = letermovir; NIMP = noninvestigational medicinal product

a: The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

b: LET IV formulation dosing volume is 250 mL and duration of infusion will be 60 minutes. LET IV will be provided as a sterile liquid concentrate for dilution (20 mg/mL), one vial to be used for the 240-mg dose and two vials for the 480-mg dose. Locally supplied sterile IV dextrose or saline diluent will be used as the placebo to LET IV as prepared by the site unblinded pharmacist.

c: The IV formulation should be switched to oral study therapy (ie, at the next planned dose) as soon as participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves.

All supplies indicated in Table 1 and Table 2 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

All placebos were created by the Sponsor to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.2.3 Participant-level Study Medication Accountability

The investigator/study coordinator will train the participant in the use of the Study Medication Diary. The participant will be instructed to record the number of tablets of study therapy taken during the study therapy period. At visits when used/unused study therapy are returned, site personnel must verify the accuracy of the dosing diary by comparing entries with amounts of returned study therapy. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the participant, and the detailed explanation must be documented in the participant's study record. The investigator/study coordinator will be responsible for transferring the appropriate information to the case report form.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study medication arms. Participants will be randomized 2:1 to receive either LET (dosage of 240 mg or 480 mg dependent on CsA status) or placebo for LET.

6.3.2 Stratification

Treatment allocation/randomization will be stratified by:

1) study center and

2) haploidentical donor (yes/no)

6.3.3 Blinding

In this study a double-blinding technique with in-house blinding will be used. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study medication administration or clinical evaluation of the participants are unaware of the intervention assignments.

Oral LET tablets will be packaged identically so that treatment blind/masking is maintained. A placebo image to LET (both 240 mg and 480 mg) will be implemented to maintain study blinding and placebo tablets will be indistinguishable from LET. Participants on CsA will receive either 1 tablet of 240 mg LET or 1 tablet of matching placebo. Participants not on CsA will receive either 480 mg LET (administered as 1 tablet of 480 mg LET or 2 tablets of 240 mg LET) or 1 or 2 tablets of matching placebo.

IV LET matching placebo (see Section 6.1) will be prepared in a blinded fashion by an unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV study therapy). The unblinded pharmacist will obtain the IV treatment assignment from IRT. The Sponsor will provide opaque covers for the IV bags in order to assist with blinding IV study therapy.

Because this is a double-blind study, the investigator, study personnel, and participant must remain blinded to the IV study therapy. In order to maintain the blinding, the unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV study therapy) will be responsible solely for the preparation of the IV study therapy. He/she will not be involved in evaluating participants for efficacy or safety. The IV study therapy will be administered by blinded personnel of the site. Refer to the Pharmacy Manual for further details.

Patients who have their treatment inadvertently unblinded will not be discontinued from the study.

6.4 Study Intervention Compliance

Interruptions from the protocol specified treatment for ≥7 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

It is important for investigators to review each medication (prescription and non-prescription) the participant is taking before starting the study and at each study visit.

- At each visit, participants should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.

Given that the lists below are not comprehensive, the investigator should use his/her medical judgment when a participant presents with a medication not on the list and consult with the Sponsor when appropriate.

6.5.1 Allowed Medications/Therapies to be Administered with Clinical and/or Drug Level Monitoring when Coadministered with Study Therapy

The following medications/therapies are allowed when coadministered with study therapy, but should be used with clinical monitoring for AEs related to these agents and/or drug level monitoring of these agents (please refer to the prescribing information of each local product circular).

Note: Since the drug-drug interactions may be different when LET is coadministered with CsA than when drugs are coadministered with LET without CsA, please refer to Section 6.5.2.2 for additional recommendations when study therapy is coadministered *with* CsA.

- **CYP3A substrates**:
  - Coadministration of LET with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates (eg, alfentanil, fentanyl, and midazolam). Therefore, frequent monitoring for adverse reactions related to these agents is recommended during coadministration.
  - Dose adjustment of CYP3A substrates with narrow therapeutic range (NTR) may be needed when coadministered with LET (a moderate CYP3A inhibitor). Please consult current prescribing information for monitoring and dosing of these products with moderate inhibitors of CYP3A.
    - Cyclosporin A (CsA): Coadministration of LET with CsA increases CsA concentrations. Frequent monitoring of CsA whole blood concentrations should be performed during and at discontinuation of LET with the dose of CsA to be adjusted as appropriate.
    - Sirolimus: Coadministration of LET with sirolimus increases concentrations of sirolimus. Frequent monitoring of sirolimus whole blood concentrations should be performed during and at discontinuation of LET with the dose of sirolimus to be adjusted as appropriate. When LET is co-administered with CsA, refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with CsA.
    - Tacrolimus: Coadministration of LET with tacrolimus increases tacrolimus concentrations. Frequent monitoring of tacrolimus whole blood concentrations should be performed during and at discontinuation of LET with the dose of tacrolimus to be adjusted as appropriate.
    - Everolimus: Coadministration of LET with everolimus may increase everolimus concentrations. Frequent monitoring of everolimus blood concentrations should be performed during and at discontinuation of LET with the dose of everolimus to be adjusted as appropriate. (**Note**: Please see Section 6.5.2.2 for recommendation of everolimus when LET is co-administered with CsA).
    - Amiodarone: LET may increase the plasma concentrations of amiodarone (CYP3A and CYP2C8 substrates). Frequent monitoring for adverse reactions related amiodarone is recommended during coadministration. Frequent monitoring of amiodarone concentrations should be performed when co-administered with LET.

- **Certain HMG-CoA reductase inhibitors (statins) as substrates of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) and/or CYP3A:**

  – Atorvastatin: The dose of atorvastatin should not exceed a daily dose of 20 mg. (**Note**: Please see Section 6.5.2.2 for recommendation of atorvastatin when LET is co-administered with CsA)

  – Fluvastatin, lovastatin, rosuvastatin, or pravastatin: The dose of fluvastatin, lovastatin, rosuvastatin, or pravastatin may need to be adjusted when co-administered with LET. Monitoring for statin-associated adverse reactions (eg, myalgias, rhabdomyolysis) is recommended during co-administration with LET.

- **Substrates of CYP2C9 and CYP2C19 (voriconazole, warfarin, phenytoin, omeprazole, and pantoprazole):**

  – Voriconazole: Co-administration of LET with voriconazole decreases the plasma concentrations of voriconazole likely due to induction of CYP2C9 and/or 2C19. If concomitant administration is necessary, close monitoring for reduced effectiveness of voriconazole is recommended.

  – Warfarin: LET may decrease the plasma concentrations of CYP2C9 and/or CYP2C19 substrates (eg, warfarin). Frequent monitoring of international normalized ratio (INR) should be performed while warfarin is co-administered with LET.

  – Proton Pump Inhibitors, omeprazole, and pantoprazole: LET may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.

- **Medications for Diabetes:**

  – Glyburide, repaglinide, or rosiglitazone: LET may increase the plasma concentrations of these diabetic medications. Frequent monitoring of glucose concentrations is recommended during co-administration with LET. (**Note**: please see Section 6.5.2.2 for recommendation of repaglinide when LET is co-administered with CsA)

6.5.2 Prohibited Medications

Medications/therapies that are prohibited during coadministration with study therapy during the time periods specified are outlined in Section 6.5.2.1. Since the drug-drug interaction on co-administered drugs may be different when LET is co-administered with CsA than when drugs are co-administered with LET without CsA, additional prohibited medications when study therapy is co-administered with CsA are outlined in Section 6.5.2.2.

Study therapy should be administered in a manner consistent with the LET local product circular, including the complete list of prohibited medications (ie, those that are contraindicated or not recommended) in the circular. The local product circular for LET supersedes this section when the product circular is more restrictive.

If there is a clinical indication for one of these or other medications specifically prohibited during the study, discontinuation from study therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study therapy requires the mutual agreement of the investigator, the Sponsor, and the participant. Given that the list below is not comprehensive, the investigator should use his/her medical judgment when a participant presents with a medication not on the list and consult with the Sponsor.

6.5.2.1 Medications Prohibited with Study Medication

- Antiviral drugs or therapies for prevention/treatment of CMV are prohibited during the study (Week 14 to 48 post-transplant), including but not limited to:
  - letermovir that is not part of study medication
  - ganciclovir or valganciclovir
  - foscarnet
  - cidofovir
  - acyclovir (at doses greater than those recommended for HSV/VZV prophylaxis, such as >3200 mg PO per day or >25 mg/kg IV per day)
  - valacyclovir (at doses greater than those recommended for HSV/VZV prophylaxis, such as >3000 mg)
  - famciclovir (at doses greater than those recommended for HSV/VZV prophylaxis, such as >1500 mg)
  - CMV immunoglobulin
  - any investigational CMV antiviral agent/biologic therapy, including CMV vaccines

    Note: these agents may be used for *other* indications while participants are on study therapy (eg, foscarnet for the treatment of HHV-6 or acyclovir for treatment of disseminated zoster)

The following medications/therapies are prohibited during the dosing period and for 14 days after study medication is discontinued:

- Investigational Agents: Unapproved investigational agents or investigational regimens involving combinations of *approved* agents are not permitted **except**
  - Investigational chemotherapy regimens involving *approved* agents and investigational antimicrobial regimens involving *approved* antibacterial/antifungal/antiviral agents, investigational radiotherapy studies, or other observational studies are allowed.
- Herbal Supplements: Herbal supplements are not permitted.
- CYP3A substrates with NTR, including but not limited to:
  - Pimozide: Concomitant administration of LET may result in increased concentrations of pimozide due to inhibition of CYP3A by LET, which may lead to QT prolongation and torsade de pointes.
  - Ergot alkaloids: Concomitant administration of LET may result in increased concentration of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by LET, which may lead to ergotism.
- Certain HMG-CoA reductase inhibitors (statins) (**Note:** See Section 6.5.2.2. for additional statins that are prohibited for use when LET is coadministered with CsA):
  - Simvastatin and pitavastatin
  - Fixed dose combinations of statins
- Strong inducers, such as rifampin, phenytoin, carbamazepine, St John's wort (Hypericum perforatum), rifabutin and phenobarbital
- Moderate inducers, such as nafcillin, thioridazine, modafinil and bosentan

6.5.2.2 Additional Medications Prohibited When Study Medication is Co-administered with CsA

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when LET is co-administered with CsA than when drugs are co-administered with LET without CsA. In addition to the prohibited medications listed above in Section 6.5.2.1, medications listed in this section are additional medications that are prohibited when coadministered with LET *and* CsA during the dosing period and for 14 days after the dosing period. When used together, they should be administered in a manner consistent with the local product circulars (for CsA and LET), including the complete list of prohibited medications including those that are contraindicated or not recommended. The

local product circular for LET supersedes this section when the product circular is more restrictive.

- Certain HMG-CoA reductase inhibitors (statins): When LET is co-administered with CsA, the magnitude of the increase in statin plasma concentrations is expected to be greater than with LET alone.

  – atorvastatin and lovastatin (**Note**: please see Section 6.5.2.1 for additional prohibited statins when coadministered with LET alone).

- Everolimus (**Note**: please see Section 6.5.1 for recommendation of everolimus when co-administered with LET alone)

- Repaglinide (**Note:** please see Section 6.5.1 for recommendation of repaglinide when co-administered with LET alone)

6.5.3 Rescue Medications and Supportive Care

In the event of clinically significant CMV infection (CMV disease or initiation of PET based on CMV viremia and the clinical condition of the participant) at any time during the 28-week post-transplant period, study therapy will be discontinued, and the participant may be treated according to the local standard of care (outside the context of the study). In this setting, any of the prohibited anti-CMV medications (outlined in Section 6.5) may be used.

6.6 Dose Modification (Escalation/Titration/Other)

See Section 4.3 for the LET dose to be used with or without co-administered CsA.

If CsA is initiated after starting study medication, the next dose of the study medication should be decreased to 240 mg once daily. If CsA is discontinued permanently or for the long term in a participant already receiving study medication, the next dose of study medication should be increased to 480 mg once daily. If CsA is temporarily withheld due to high levels detected by therapeutic blood monitoring, the dose of study medication need not be adjusted.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention /randomization schedule for the study to unblind participants and to unmask study medication identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to

unblind participants and to unmask study medication identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the investigational medicinal product (IMP) to provide the following advice:

"You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug letermovir as much as possible. You did not receive the active drug letermovir as manufactured by MSD."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.

- The investigator feels it is in the best interest of the participant to discontinue.
- The participant develops clinically significant CMV infection as determined by the investigator (Section 4.2.1.3).
- The participant develops one of the following:
  - Both moderate hepatic insufficiency (Child-Pugh Class B; Sections 8.3.4 and 10.8) and moderate-to-severe renal insufficiency (defined as CrCl <50 mL/min as calculated by the Cockcroft-Gault equation),

    OR

  - Severe hepatic insufficiency (Child-Pugh Class C; Sections 8.3.4 and 10.8)
- Needs dialysis or develops end-stage renal impairment with creatinine clearance ≤10 mL/min as calculated by the Cockcroft-Gault equation as follows:

  Creatinine Clearance (Males) = $\frac{\text{weight in kg} \times (140 - \text{age in years})}{72 \times \text{serum creatinine in mg/dL}}$

  Creatinine Clearance (Females) = 0.85× the value obtained with formula above

  Note: Child-Pugh class (see Appendix 8) and creatinine clearance using the Cockcroft-Gault equation should be assessed at the Day 1 and every visit until the study medication is discontinued (including at the CMVi or Early discontinuation visit if study medication is being discontinued at those visits) in order to ensure timely discontinuation of study medication.
- The participant **may be** discontinued from study medication for any of the following reasons:
- Any AE/SAE assessed by the investigator as related to study therapy. The investigator may continue the participant in the study if it is deemed to be in the best interest of the participant to stay on study therapy.
- Failure to comply with the dosing, evaluations, or other requirements of the study.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, does not allow the participant to adhere to the requirements of the protocol (eg, if there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required [see Section 6.5]).

For participants who are discontinued from study medication but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Note: Participants who have their treatment unblinded should not be discontinued from the study.

Participants may be allowed to begin study medication again if deemed medically appropriate unless the participant's treatment assignment has been unblinded by the investigator, delegate, and/or nonstudy treating physician. There may be instances where confirmatory central laboratory test results for CMV DNA PCR results obtained on the day of PET initiation may be CMV DNA undetectable or detected, but not quantifiable, and the investigator may wish to discontinue PET. The decision to stop PET resides with the investigator caring for the subject. Therefore, in the event the confirmatory CMV DNA sample at PET initiation is CMV DNA undetectable or detected, but not quantifiable, the Sponsor will allow for study therapy to be restarted at the investigator's discretion, once PET is discontinued. In such instances, study therapy should be restarted within 7 days from the date on which study therapy was stopped**. It is important to note that the status of the subject's study therapy in IRT should NOT be changed until the CMV DNA PCR result is confirmed and the investigator is certain that study therapy will be permanently discontinued.**

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 255 mL; see Appendix 2 (Section 10.2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at screening.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement. Prior medications such as antivirals, chemotherapy agents, and immunosuppressant agents taken by the participant 30 days prior to screening should be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the participant during the study treatment through 2 weeks after the study medication is discontinued. In addition, anti-CMV medications (including LET that is not part of the study medication, ganciclovir, valganciclovir, acyclovir, valacyclovir, famciclovir, foscarnet, cidofovir) administered for treatment of CMV disease or for initiation of PET, and all drug/biologic therapies used to prevent/treat GVHD should be recorded at every visit through Week 48 post-transplant (Visit 17). During the follow-up period through Week 48, concomitant medication review and recording of data is outlined in data entry guidelines.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment /randomization number. The treatment /randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment /randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment /randomization number.

8.1.8 Study Intervention Administration

The first dose of study intervention will be administered at the study site at Visit 2 (Day 1; ~Week 14 post-transplant). Subsequent dosing will be performed once daily by the participant (ie, unsupervised at his/her home) at approximately the same time each day.

For participants who develop a condition that interferes with their ability to swallow, or a condition that interferes with the absorption of the oral formulation (eg, vomiting, diarrhea, or a malabsorptive condition), a LET IV formulation is available for those participants randomized to LET and IV placebo (saline or 5% dextrose) would be administered to those randomized to placebo. IV administration is for short-course administration (up to approximately 4 weeks). The study pharmacist will be responsible solely for the preparation of the IV study medication. Site personnel will administer the IV study medication through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter, using only IV bags and infusion set materials that are diethylhexyl phthalate (DEHP)-free. Refer to the Pharmacy Manual document for further details.

8.1.8.1 Timing of Dose Administration

Study therapy should be administered/taken at the same time each day. Tablets are to be swallowed whole (ie, no crushing or chewing the tablet is allowed). Study therapy may be administered with or without food (please refer to Section 5.3.1 for food restrictions applicable to those participants who are taking concomitant CsA).

If a participant misses a dose, the missed dose should be given as soon as possible during the same day. If more than 18 hours have gone by after the regular dosing time, then the missed dose should be skipped, and the normal dosing schedule should be resumed. The next dose should not be doubled in order to “make up” what has been missed.

If a participant vomits within 2 hours of an oral administration, the full oral dose can be repeated one time within 6 hours after vomiting. If a participant vomits and it has been longer than 2 hours from the time of oral administration, the dose should not be repeated. Take the next dose at the usual time.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Early Discontinuation Visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 and Visit Requirements as outlined in Section 1.3 (SoA).

8.1.10 Participant Blinding/Unblinding

STUDY MEDICATION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and /or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study medication, the reason thereof, etc, in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

8.1.11 Domiciling

Not applicable.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 CMV DNA PCR Testing

Protocol-specified CMV DNA levels will be drawn at prespecified clinical visits and the CMV Infection Visit as indicated in the Study SoA (Section 1.3) and sent to the **central laboratory** where CMV DNA PCR testing will be performed using a quantitative CMV DNA PCR assay at the central laboratory In this study, CMV DNA levels may be monitored using local laboratory results for the clinical management of participants any time during the study. It is **MANDATORY**, however, to collect and send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory **immediately prior to** (ie, on the day of) initiating PET or treatment for confirmed or suspected CMV disease (CMV infection visit). (Note: for any site in Japan where a positive local pp65 antigen test is used to drive the decision to initiate anti-CMV therapy, in addition to a confirmatory CMV DNA PCR testing, a blood sample must be collected for confirmatory local pp65 antigen testing prior to initiating PET; the confirmatory test results are not required for initiating PET.)

In the event test results from the central laboratory are not available within the time frame the investigator wishes to initiate anti-CMV therapy (including PET), the investigator may use a positive local laboratory test (CMV DNA PCR or pp65 antigen only) result in order to make the decision. However, as described above, a confirmatory plasma samples for CMV DNA PCR testing must also be sent to the central laboratory prior to initiating PET. The local laboratory result must also be reported in such instances.

In the event that the confirmatory result obtained on the day of anti-CMV treatment (including PET) initiation is **NOT** available (eg, sample is lost or mishandled by the investigator site prior to shipment, or is inadequate upon receipt at the central laboratory), a subsequent sample must be obtained and sent to the central laboratory within 48-72 hours after initiation of anti-CMV treatment. Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

Assessment of CMV Disease

CMV disease will be assessed at every visit from screening through Week 48 post-transplant. Diagnostic criteria for the evaluation of CMV infection are outlined in Appendix 7. If CMV disease is suspected, site should perform the CMV Infection Visit instead of the scheduled visit assessments (see Section 1.3, Schedule of Activities). The investigator will ensure that clinical information, radiology results, and specimens for the appropriate diagnostic tests

(including, but not limited to, viral culture, histopathology, immunohistochemical analysis, in situ hybridization, CMV DNA PCR) as outlined in Appendix 10.7 will be collected.

8.2.2 CMV DNA Resistance Analysis

Sample collection, storage, and shipment instructions for plasma samples will be provided in the central laboratory manual.

CMV DNA sequence analysis will be performed on samples from participants who meet the criteria for clinically significant CMV infection. Resistance to LET will be assessed by genotypic analysis of the CMV terminase complex genes (UL56, UL89, and UL51) in DNA extracted from plasma samples collected as indicated in the Schedule of Activities (Section 1.3). All CMV resistance genotyping samples with detectable CMV DNA will be analyzed by next-generation sequencing technology through an established contract laboratory with validated protocols in place. The resistance genotyping assay is validated for plasma samples containing 500 copies/mL or higher of CMV DNA with a sensitivity cutoff of 5% to detect minor variants. If multiple CMV-positive resistance samples are collected, the last on-therapy and follow-up samples will be prioritized for resistance analysis.

Phenotypic analysis may be performed on any UL56, UL89, or UL51 DNA sequences which encode amino acid substitutions that have not been previously characterized for LET susceptibility.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 10.2 (Appendix 2).

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

On Day 1 (post-transplant Week 14), a complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard.

After randomization (Day 1), the physical examination does not need to be performed at every visit; a targeted physical examination should be performed only if a participant has any complaints. The timing of physical examinations is indicated in the Study SoA (Section 1.3).

Height and weight will be measured and recorded per the SoA.

8.3.2 Vital Signs

Vital signs will be assessed at the time points indicated in the SoA (Section 1.3) and will include the following assessments:

- Body temperature (oral preferred, see below), heart rate respiratory rate, and blood pressure will be assessed. NOTE: Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, temporal, or axillary temperatures may be taken.

- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.3.3 Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Participants should be shaved (if necessary) for proper lead placement. Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained.

8.3.4 Child-Pugh Score

The Child-Pugh score will be assessed as indicated in the Study SoA (Section 1.3) according to Appendix 8. At the screening visit, the clinical assessment and the central laboratory parameters (total bilirubin, albumin, and PT/INR) obtained at that visit will be used to calculate the Child-Pugh score. Thereafter, at each scheduled assessment of the Child-Pugh score, the clinical assessment at the scheduled study visit and the most recently collected and available local laboratory parameters (total bilirubin, albumin, and INR) obtained at the corresponding scheduled study visit, or up to one week prior to the scheduled study visit, will be used to calculate the Child-Pugh score. As stated in Section 7.1, a participant must be discontinued from study treatment but continue to be monitored in the study if the participant develops both moderate hepatic insufficiency (Child-Pugh Class B) and moderate-to-severe renal insufficiency (defined as CrCl <50 mL/min as calculated by the Cockcroft-Gault equation; see Section 5.2), or develops severe hepatic insufficiency (Child-Pugh Class C).

8.3.5 Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the

underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator. Thereafter, only SAEs considered to be drug-related or leading to death should be reported through Week 48 post-transplant.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through 14 days after last dose of study medication**	**Reporting Time Period: From 14 days after last dose of study medication until study completion**	**Timeframe to Report Event and Follow-up Information to SPONSOR:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Report only if: - drug-related. OR -SAEs leading to death, regardless of causality	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through 14 days after last dose of study medication	**Reporting Time Period:** From 14 days after last dose of study medication until study completion	Timeframe to Report Event and Follow-up Information to SPONSOR:
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose		Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An elevated AST or ALT laboratory value that is ≥3× ULN and an elevated total bilirubin laboratory value that is ≥2× ULN and, at the same time, an alkaline phosphatase laboratory value that is <2× ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

* Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than two times the prescribed dose specified in Section 6.6 (Dose Modification [Escalation/Titration/Other]).

Sponsor does not recommend specific treatment for an overdose. Overdose during the study will be a reportable safety event (see Section 8.4.1 and Appendix 3 for further details).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

PD parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Biomarkers

CMV-specific T-cell responses will be measured using the QuantiFERON-CMV assay [Becke, S., et al 2010] [Goldner, T., et al 2011] at various time points through Week 48 post-transplant using plasma samples. The proportion of participants with positive QuantiFERON-CMV assay results will be correlated with the incidence of clinically significant CMV infection through Week 48 post-transplant and assessed as an exploratory endpoint. The central laboratory based QuantiFERON-CMV assay results will not be shared with the respective site investigators.

8.11 Health Outcomes Assessment

All-cause mortality, all rehospitalizations and CMV-related rehospitalizations, GVHD, select opportunistic infections, IV medication other than LET use, and recurrent CMV infection will be measured to assess healthcare resource utilization. The data collected may be used to conduct exploratory economic analyses. Protocol-mandated procedures, tests, and encounters are excluded.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Approximately 14 days prior to treatment allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 5.1 and 5.2. Screening procedures may be repeated after consultation with the Sponsor.

Human immunodeficiency virus (HIV) antibody test results documented at any time prior to screening of the participant will be acceptable; a copy of this HIV report must be available. (See Exclusion Criterion #10 in Section 5.2). If documentation of a previous HIV test is not available, the HIV antibody test must be conducted using the central or local laboratory. Hepatitis B and hepatitis C screening should only be performed if not previously documented within the last 6 months. If hepatitis C virus antibody is positive, HCV RNA PCR results should be provided (or, if not available, HCV RNA PCR testing will be performed by the central or local laboratory).

8.12.2 Treatment Period

Study medication (LET/Placebo) may begin as early as 14 weeks ± 1 week post-transplant. Study medication will be dispensed every 2 weeks and continue through Week 28 (~200 days) post-transplant. The treatment period is through Week 28 post-transplant regardless of when study medication is discontinued. Study visits will occur every 2 weeks through Week 28 (~200 days) post-transplant.

The Day 1 Visit (as shown in the SoA, Section 1.3) will be the day the participant is randomized and study medication is initiated. Study medication will continue for 14 weeks through the End of Treatment Visit at Week 28 (~200 days) post-transplant.

All procedures listed under the study visits in the SoA (Section 1.3) will be performed at the corresponding visit. After allocation, the physical examination does not need to be performed at every visit; a targeted physical exam should be performed only when clinically indicated.

8.12.2.1 Day 1 Visit

Day 1 procedures/assessments listed on the SoA (Section 1.3) must be performed prior to initiation of study medication.

For female participants of childbearing potential, a urine or serum pregnancy test will be performed at the site prior to the initiation of study medication. If the urine or serum pregnancy test result is negative, the participant will be eligible for allocation and the remainder of the Day 1 testing/procedures will be performed. If the urine or serum pregnancy result is positive, the participant must not be randomized.

8.12.2.2 Study Medication Administration

The site pharmacist or study coordinator will contact the IRT at all dispensing visits for assignment of the study medication to be administered. Sites should not contact the IRT for study medication administration until the participant has met all criteria for the study and is ready to receive the first dose of study medication on Day 1.

The first dose of study medication (LET or placebo to LET) will be administered at the trial site with monitoring by investigative site personnel at the Day 1 Visit (Visit 2; Week 14 post-transplant). For participants who cannot swallow and/or have a condition that may interfere with the absorption of the oral formulation at or after randomization/Day 1, a LET IV formulation is available for those participants randomized to LET and IV placebo (saline or 5% dextrose) would be administered to those randomized to placebo. Participants should be switched from the IV formulation back to oral study therapy as soon as such participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves and the appropriate oral study drug supply may be obtained for the participant. Use of the IV formulation should generally be limited to 4 weeks or less in duration per participant. However, it will be left to the investigator's discretion to continue IV administration beyond 4 weeks, if the benefit/risk ratio supports continued administration.

Participants who are not on CsA will receive LET 480 mg QD or placebo to LET QD given orally. Participants who are receiving concomitant CsA will receive oral formulation of LET 240 mg QD or placebo to LET QD. Participants requiring IV formulation (LET or placebo to LET) who are not on CsA will receive 480 mg IV QD (Section 6.1). Participants requiring the IV formulation of LET or placebo to LET who are on concomitant CsA will receive 240 mg QD of IV study medication (ie, participants randomized to placebo who require IV administration will be able to receive IV administration of placebo).

If CsA is initiated after starting study medication, the next dose of the study medication should be decreased to 240 mg once daily. If CsA is discontinued permanently or for the long term in a participant already receiving study medication, the next dose of study medication should be increased to 480 mg once daily. If CsA is temporarily withheld due to high levels detected by therapeutic blood monitoring, the dose of study medication need not be adjusted (see Section 6.6).

The participant will be trained in the use of the Study Medication Diary. He/she will be instructed to enter the number of tablets of study medication taken during the study treatment period. IV study medication will be recorded by the unblinded pharmacist or study personnel in the CRF.

8.12.3 Optional Nurse Visit and Telephone Visit (Weeks 32 and 36 Only)

A visiting nurse service may be utilized (if locally available and approved for use) at Visit 11 (Week 32) and Visit 13 (Week 36) in coordination with an investigator CMV assessment by phone. If a visiting nurse service is utilized, the investigator phone call should occur on the same day as the nurse visit, or as soon as possible. Refer to the nursing manual for additional details.

8.12.4 Follow-up Period/Visits

As stated in Section 8.12.2, participants will receive study medication for 14 weeks through Week 28 (~200 days) post-transplant. After the last day of study medication, participants will be followed via study visits from Week 30 to Week 48 post-transplant. These visits will occur every 2 weeks from Week 30 to Week 40 and every 4 weeks from Week 40 to Week 48 and all procedures listed in the SoA (Section 1.3) corresponding to the visits will be performed.

All participants will continue to be assessed for CMV infection/disease through Week 48 post-transplant and CMV DNA PCR should be tested at the central laboratory as per the SoA (Section 1.3).

Adverse event monitoring should include the collection of all AEs while on study medication and for 14 days following completion of study medication in all participants. Thereafter, only drug-related SAEs and SAEs leading to death will be collected through Week 48 post-transplant.

8.12.5 Discontinued Participants Continuing to be Monitored in the Study

8.12.5.1 Discontinuation of Study Medication due to CMV Infection

For participants who develop CS-CMVi through Week 28 post-transplant**,** the participant should have a CMV Infection Visit. At this visit, study medication should be discontinued (if applicable) and all procedures as outlined in the Schedule of Activities (Section 1.3), including collection of a blood sample, should be performed immediately prior to the initiation PET or treatment of CMV disease. Additionally, a repeat plasma sample for CMV viral resistance testing should be collected at the next scheduled visit after the CMV Infection Visit (Section 8.2.2).

Such participants **will continue to be followed in the study** (despite discontinuing study medication and initiating anti-CMV therapy) and complete all remaining study visits (including all subsequent treatment period visits).

8.12.5.2 Discontinuation for Reasons Other Than CMV Infection

Study Medication Discontinuation

Participants who discontinue study medication prior to the last scheduled treatment visit for reasons other than CS-CMVi **will continue to be followed in the study** and complete all remaining study visits regardless of when cessation of study medication occurs. All specified procedures will be completed for these participants through Week 28 post-transplant during the treatment period (with the exception of study medication administration, and Study Medication Diary review); and through Week 48 post-transplant in the follow-up period as outlined in the SoA (Section 1.3).

Early Study Discontinuation

The Early Discontinuation Visit will also be performed for all participants who prematurely discontinue the study (ie, withdraw consent) prior to the Week 48 post-transplant visit. It is very important to ensure that all procedures, as outlined in the Study SoA (Sections 1.3), are performed for such participants at this visit prior to discontinuing from the study. A plasma sample for CMV DNA PCR testing should be collected at this visit.

8.12.6 Survival Status

Updated survival status may be requested at any time, both during study conduct or after study completion, or after a subject discontinues from the study. All participants or their contacts may be contacted for their survival status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT)
Treatment Assignment	Approximately 216 participants who have already received ~100 days of LET will be randomized in a 2:1 ratio with 144 receiving LET prophylaxis for an additional 100 days (200-day arm) and 72 receiving placebo (100-day arm). Treatment allocation / randomization will be stratified by study center and haploidentical donor (yes/no).

Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant
Key Secondary Endpoints	1. Safety and tolerability of LET 2. Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant and from Week 14 post-transplant through Week 48 post-transplant 3. Time to clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant 4. Proportion of participants with PET for documented CMV viremia from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant 5. Proportion of participants with of all-cause mortality from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant 6. Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary hypothesis will be evaluated by comparing LET to placebo with respect to the proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant using the stratified Mantel-Haenszel method [Koch, G. G., et al 1990] when LET prophylaxis is extended from 100 to 200 days post-transplant.
Statistical Methods for Key Safety Analyses	95% CIs (Tier 2 endpoints) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	Periodic safety analyses will be conducted for the accruing data and will be reviewed by an external Data Monitoring Committee (DMC) at regular intervals as outlined in the DMC charter. This will supplement routine in-house medical monitoring. No formal interim analyses for efficacy are planned for this study. However, efficacy data will be included as part of the periodic safety reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment to allow for an assessment of benefit-risk.
Multiplicity	No formal efficacy analyses will be provided and there is no intention of stopping the trial due to overwhelming efficacy at any of these safety reviews. Nevertheless, since unblinded efficacy data are being periodically reviewed, using a Haybittle-Peto α spending approach, a small amount of alpha ($\alpha = 0.0001$) will be allocated for each of these looks before testing the primary efficacy hypothesis at Week 28 post-transplant. An allowance will be made such that a total of up to three of these unblinded efficacy reports may be presented at these periodic safety reviews. The final analysis can still be tested at 2.5% level without inflating Type-I error.

Sample Size and Power	The planned sample size is 216. For the proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant, the study has 80% power at an overall one-sided 2.5% alpha-level to demonstrate that LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant, if the incidence rates of CS-CMVi are 8% for LET (200-day arm) and 22% for placebo (100-day arm).

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule for study treatment assignment. Randomization will be implemented in the IRT.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

9.4.1.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.2.1.1.

The primary efficacy endpoint will be the proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant, defined as the occurrence of either one of the following outcomes:

- onset of CMV end-organ disease (proven or probable)

  OR

- initiation of anti-CMV PET with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia and the clinical condition of the participant

CMV end-organ disease will be determined using the definitions in Appendix 7 and confirmed by an independent, blinded CAC. The adjudication of cases by the CAC (ie, the final CAC assessment) will take precedence over the investigator's assessment for the purpose of analysis. Only the CAC-confirmed (proven or probable) cases of CMV end-organ disease will be included in the CMV end-organ disease category. However, investigator-assessed CMV end-organ disease cases that were not confirmed by the CAC but in whom anti-CMV therapy was initiated (in the setting of documented CMV viremia at a central laboratory) will be included in the initiation of PET category and, therefore, qualify as having clinically significant CMV infection. Concordance/discordance between CAC and investigator assessment will be summarized.

Documented viremia is defined as any quantifiable CMV viral DNA on a confirmatory sample obtained immediately prior to (ie, on the day of) the initiation of treatment for CMV disease or PET, as measured by the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) System in the central laboratory. In the event that the confirmatory result is not available, a subsequent central laboratory result collected from a sample obtained within 7 days will be used. Initiation of anti-CMV therapy without documented CMV viremia (using the central laboratory) will not be considered as a case for clinically significant CMV infection. Similarly, quantifiable CMV viral DNA alone without initiation of anti-CMV therapy will not be considered as a case for clinically significant CMV infection. If there are cases where anti-CMV therapy is initiated with no quantifiable CMV viral DNA using the central laboratory data, a sensitivity analysis will be provided using the local laboratory results.

The secondary efficacy endpoints are:

1. Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant and from Week 14 post-transplant Week 48 post-transplant. This endpoint will use the same definition of clinically significant CMV infection as in the primary efficacy endpoint.

2. Time to onset of clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant.

   The time to onset of clinically significant CMV infection will be calculated in days, from the day of transplant to the day of onset of CMV end-organ disease or to the day of initiation of anti-CMV PET. For cases where CMV end-organ disease is confirmed by the CAC, date of the first diagnostic test (including, but not limited to, radiology tests, viral culture, histopathology, immunohistochemical analysis, in situ hybridization, and CMV DNA PCR) will be identified by the CAC as part of their medical review and used as the time of onset of CMV end-organ disease. For cases where anti-CMV PET is initiated in the setting of documented viremia (including those applicable cases where CMV end-organ disease was not confirmed by the CAC), the start date of anti-CMV therapy will be used. If both criteria for clinically significant CMV infection are met, the time to onset will be calculated from the day of transplant to the earlier day on which one of the criteria is met.

3. Proportion of participants with initiation of PET for documented CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant. This endpoint will use the same definition for initiation of PET for documented CMV viremia as in the primary efficacy endpoint.

4. Proportion of participants with all-cause mortality from Week 14 post-transplant through post-Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

5. Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant. The time to all-cause mortality will be calculated in days, from the day of transplant to the day of death.

9.4.2 Safety Endpoints

An initial description of safety measures is provided in Sections 8.3 and 8.4.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values and vital signs. All AEs will be collected through 14 days after completion of treatment period. Thereafter, all drug-related SAEs and SAEs leading to death will be collected through Week 48 post-transplant.

9.4.3 Exploratory Endpoints

1. Proportion of participants with CMV end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant

2. Time to CMV end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant. The time to CMV end-organ disease will be calculated in days, from the day of transplant to the day of CMV end-organ disease.

3. Proportion of participants with documented CMV viremia ≥300 copies/mL from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

4. The time to documented CMV viremia ≥300 copies/mL from Week 14 post-transplant through Week 48 post-transplant.

5. Proportion of participants with select opportunistic infections other than CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

6. Proportion of participants with GVHD from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

7. Proportion of participants with all rehospitalizations and rehospitalizations for CMV infection/end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

8. Days on intravenous medications other than LET from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

9. Proportion of participants with recurrent CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

10. Proportion of participants with CMV-specific T cell responses (positive, indeterminate, or negative) as measured by the release of γ-interferon using the QuantiFERON-CMV assay.

11. Antiviral resistance to LET in prophylaxis failures.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who received at least one dose of study treatment.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values may be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α=0.025 (1-sided) level.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the supplemental SAP.

Missing Data Handling

There are three types of missing values:

- Intermittent missing values due to a missed or skipped visit.
- Monotone (non-intermittent) missing due to premature discontinuation from the study: viremia at study discontinuation.
- Monotone missing due to premature discontinuation from the study: no viremia at study discontinuation.

Table 4 provides a summary of approaches to handle missing values.

Table 4 Summary of Approaches to Handle Missing Values

Approach	**Intermittent Missing**	**Monotone Missing**	
		No Viremia at Study Discontinuation	Viremia at Study Discontinuation
OF	No failure	No failure	Failure
NC=F	Failure	Failure	Failure
DAO	Excluded	Excluded	Excluded
F = failure; NC = Non-Completer; OF = Observed Failure; DAO = Data-As-Observed			

The primary missing data approach will be the Observed Failure (OF) approach in order to obtain an estimate of the proportion of clinically significant CMV infection in participants who receive prophylaxis study treatment. Using this approach, participants who develop clinically significant CMV infection or participants who discontinue prematurely from the study with viremia will be counted as failures, and participants who discontinue prematurely from the study for any reason without viremia or those who are missing data at the time points of interest are not considered failures. Imputing all participants who discontinue from the study prematurely without viremia as failures is likely to substantially overestimate the proportion of participants with clinically significant CMV infection.

Two secondary missing data approaches will be used for supportive analyses. The first is the Data-As-Observed (DAO) approach. In the DAO approach, any participant with missing value for a particular endpoint, either because they discontinued from the study without the endpoint or are missing data at the key time point (eg, missed visit, missing lab value), will be excluded from the analysis. The second approach is the Non-Completer = Failure (NC=F) approach, which provides the worse-case scenario estimate of the proportion of clinically significant CMV infection. Non-completers refer to participants who prematurely discontinue from the study for any reason without having developed CMV infection or participants who are missing data at the time points of interest. These participants will be considered failures using the NC=F approach.

Primary Efficacy Analysis

To test the primary hypothesis that LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant, the stratum-adjusted Mantel-Haenszel method (with continuity correction) will be used to compare the proportion of subjects with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant between the two treatment groups [Koch, G. G., et al 1990]. The stratification factor of haploidentical donor (yes/no) will be included in the primary efficacy analysis. Cochran Mantel-Haenszel weights will be used to calculate the overall between-group differences across strata. LET is concluded superior to placebo if 1-sided p-value is less than or equal to 0.0249 (see Section 9.8 for alpha adjustment). Due to the anticipated large number of study centers, study center will not be included as a stratification factor in the primary efficacy analysis but may be explored as a sensitivity analysis. The primary efficacy analysis will be performed on the FAS population. A sensitivity analysis excluding those subjects who had quantifiable CMV viral DNA on Day 1 will be provided. The primary missing data approach will be the OF approach; supportive analyses using different missing data approaches will also be conducted (see Table 5).

Two additional sensitivity analyses for the primary endpoint will be performed to assess 1) the proportion of participants with either CMV disease or PET initiation based on CMV viremia ≥300 copies/mL (ie, participants who initiated PET without meeting the threshold will not be considered a case of CS-CMVi), and 2) the proportion of participants with either CMV disease or CMV viremia of ≥300 copies/mL regardless of whether PET was initiated.

Since the use of a therapy with anti-CMV activity may confound the results of this study, an additional sensitivity analysis will be conducted in which participants who start a therapy with anti-CMV activity will be censored at the time they begin such therapy. Subjects with CS-CMVi prior to taking a therapy with anti-CMV activity will be classified as having CS-CMVi. Those who did not have CS-CMVi prior to taking a therapy with anti-CMV activity (including subjects who subsequently develop CS-CMVi) will be classified as not having CS-CMVi and censored at the time they started taking the anti-CMV therapy.

Secondary Efficacy Analyses

To assess the difference in the proportion of participants with the following secondary endpoints:

- clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant
- clinically significant CMV infection from Week 14 post-transplant through Week 48 post-transplant
- initiation of PET for documented CMV viremia from Week 14 post-transplant through Week 28 post-transplant
- initiation of PET for documented CMV viremia from Week 14 post-transplant through Week 48 post-transplant
- all-cause mortality from Week 14 post-transplant through Week 28 post-transplant
- all-cause mortality from Week 14 post-transplant through Week 48 post-transplant

Similar to the primary endpoint, 95% confidence interval for the difference in proportion between treatment groups will be calculated using the stratum-adjusted Mantel-Haenszel method with stratification by haploidentical donor (yes/no) [Koch, G. G., et al 1990]. A nominal p-value will be provided to assess the strength of evidence of the effect.

Time to onset of clinically significant CMV infection from Week 14 post-transplant through 28 weeks post-transplant and from Week 14 post-transplant through Week 48 post-transplant will be estimated using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted by treatment arm and a nominal p-value for the between-arm difference in time to onset of clinically significant CMV infection will be provided using the stratified log-rank test stratified by haploidentical donor (yes/no). Observations will be censored at last assessment. Time to all-cause mortality from Week 14 post-transplant through 28 weeks post-transplant and from Week 14 post-transplant through Week 48 post-transplant will be estimated similarly.

Table 5 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach*
Primary Endpoint				
Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant	P	Stratified M&H‡	FAS	OF
	S	Stratified M&H‡	FAS	DAO
	S	Stratified M&H‡	FAS	NC=F
Secondary Endpoints				
Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant and from Week 14 post-transplant through Week 48 post-transplant	P	Stratified M&H‡	FAS	OF
	S	Stratified M&H‡	FAS	DAO
	S	Stratified M&H‡	FAS	NC=F
Time to onset of clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	P	Kaplan-Meier	FAS	Censored at last assessment
Proportion of participants with initiation of anti-CMV PET for CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant weeks	P	Stratified M&H‡	FAS	OF
	S	Stratified M&H‡	FAS	DAO
	S	Stratified M&H‡	FAS	NC=F
Proportion of participants with all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant weeks	P	Stratified M&H‡	FAS	OF
Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant	P	Kaplan-Meier	FAS	Censored at last assessment

† P=Primary approach; S=Supportive approach.

‡ Stratum-adjusted Mantel-Haenszel method with stratification by haploidentical donor (yes/no)

* OF=observed failure; DAO=data-as-observed; NC=F = non-completers equal failure

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs measurements.

The analysis of safety results will follow a tiered approach (Table 6). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory, and vital signs parameters are either prespecified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as LET has not been associated with any significant AEs that need to be characterized compared to placebo.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events (Miettinen and Nurminen [M&N] method) [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 8 participants in the 200-day arm or 2 participants in the 100-day arm exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The thresholds of events were chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when fewer participants per group, respectively, experience events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 8 or more participants in the 200-day arm or 2 participants in the 100-day arm, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE†	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Discontinuation due to AE	X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥8 participants in the 200-day arm or ≥2 participants in the 100-day arm)	X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence ≥1 participant in either arm)		X
	Change from Baseline Results (Labs, Vital Signs)		X

95% CIs will be based on the method of Miettinen and Nurminen (1985).

† Indicates broad AE category of the number of participants reporting any adverse event

Note: AE=adverse event; CI =confidence interval; SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

9.7 Interim Analyses

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study.

To supplement the routine safety monitoring outlined in this protocol, an external DMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to the EOC (see Appendix 1; Section 10.1.4 [Committees Structure – Executive Oversight Committee]). No formal interim analyses for efficacy are planned for this study. However, to allow for an assessment of benefit-risk, efficacy data will be included as part of the periodic safety reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment. The DMC will monitor the trial with suggested periodic reviews occurring approximately every 6 months. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which

individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the DMC charter.

Treatment-level results from the interim analysis will be provided to the DMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.8 Multiplicity

The DMC will be provided with unblinded descriptive summaries of the efficacy data at their periodic safety reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment for an assessment of benefit-risk. No formal efficacy analyses will be provided and there is no intention of stopping the trial due to overwhelming efficacy at any of these safety reviews. Nevertheless, since unblinded efficacy data are being periodically reviewed, using a Haybittle-Peto α-spending approach, a small amount of alpha ($\alpha = 0.0001$) will be allocated for each of these looks before testing the primary efficacy hypothesis at Week 28 post-transplant. An allowance will be made such that a total of up to three of these unblinded efficacy reports may be presented at these periodic safety reviews. The final analysis can still be tested at 2.5% level without inflating Type-I error.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analysis

Data from P001 in participants who were in the high-risk stratum as defined in P001 were used to estimate the clinically significant CMV infection rates for this study, since these populations are similar between the two studies. The 100-day arm in this study is similar to those in the high-risk stratum on LET who completed treatment without any clinically significant CMV infection in P001, in which 20.5% had clinically significant CMV infection after completing treatment and through Week 24 post-transplant. This would be expected to be slightly higher through Week 28 post-transplant leading to an estimate of 22% for through Week 28 post-transplant in this study. The event rate for the 200-day arm is expected to be similar to the event rate at the end of LET treatment at Week 14 post-transplant for participants in the P001-defined high-risk stratum, which was 10.8% (11/102, including 4 participants who had discontinued LET due to AEs and then developed CS-CMVi). Since this study will enroll participants who will have already tolerated LET for 100 days, it is expected that a lower percentage of patients will discontinue treatment due to AEs, thus lowering the overall failure rate in the 200-day arm to ~8%.

This study will randomize a total of 216 participants (in a 2:1 ratio) with 144 in the LET (200-day) arm and 72 in the placebo (100-day) arm which will have 80% power at an overall one-sided, 2.5% alpha-level, to demonstrate the primary hypothesis that extending LET prophylaxis to 200 days post-transplant is superior to 100 days of LET prophylaxis post-transplant in the prevention of clinically significant CMV infection. This assumes incidence rates of CS-CMVi of 8% for LET (200-day arm) and 22% for placebo (100-day

arm). The calculation is based on normal approximation by Pearson Chi-square test for proportion difference without continuity correction and is carried out using (SAS v9.4). The minimum criterion for success is that the upper bound of 95% CI of difference < 0. Given the assumed response rate in 200-day arm, this may occur when the observed difference between treatment groups is approximately -10% or smaller. Table 7 presents the power under various assumptions of rates in the two arms using the OF approach for missing data.

Table 7 Power(%) Under Various Assumptions (With 144 Participants Randomized in 200-day Arm and 72 in 100-day Arm)

Rate in Placebo (100-day) Arm	Rate in LET (200-day) Arm					
	6	7	8	9	10	11
18	76	67	58	49	39	31
20	85	78	70	62	53	44
22	91	86	80	73	65	57
24	95	92	88	82	76	69
26	97	65	93	89	84	79
28	99	98	96	94	90	86

9.9.2 Sample Size and Power for Safety Analysis

The probability of observing at least one of a particular AE in this study depends on the number of participants treated and the underlying percentage of participants with that AE in the study population. If the underlying incidence of a particular AE is 1% (1 of every 100 participants receiving the drug), there is a 52% chance of observing at least one of that particular AE among 72 participants in the placebo (100-day) arm or a 76% chance of observing at least one of that particular AE among 144 participants in the LET (200-day) arm. If no AE of that particular type are observed among the 144 participants in the LET (200-day) arm, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <2.5% (one in every 40 participants).

The estimate of and the upper bound of the 95% confidence interval for the underlying percentage of participants with a particular AE given various hypothetical observed number of participants with the AE are provided in Table 8. The calculation is based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934] and is carried out using SAS v9.4.

Table 8 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs

	Hypothetical Number of Participants with an AE (Estimate of Incidence, %)	95% Upper Confidence Bound†
N=72	0 (0)	5.0
	2 (2.8)	9.7
	4 (5.6)	13.6
	6 (8.3)	17.3
N=144	0 (0)	2.5
	4 (2.8)	7.0
	8 (5.6)	10.7
	12 (8.3)	14.1
† Based on the two-sided exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).		

9.10 Subgroup Analyses

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-arm treatment effect (with a nominal 95% CI) for the primary efficacy endpoint will be tabulated and plotted within each category of the following classification variables:

- Age category (≤65 versus >65 years)
- Sex (female, male)
- Race (white, black, Asian, other)
- Systemic steroid exposure within 6 weeks prior to randomization (yes, no)
- Donor type (mismatched related, matched unrelated, mismatched unrelated)
- Haploidentical donor (yes, no)
- Cord blood (yes, no)
- T-cell depleted grafts (yes, no)
- Receipt of anti-thymocyte globulin (yes, no)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. Other clinically relevant variables may be identified for which additional subgroup analyses may be performed. Subgroup analyses will not be conducted in categories that have less than 10% of the participants in either LET or placebo group (ie, no estimate of treatment difference and confidence intervals will be provided).

9.11 Compliance (Medication Adherence)

Study medication data for LET (200-day arm) and placebo (100-day arm) will be collected during the study. A day within the study will be considered an "On-Therapy" day if the participant takes at least 1 dose. For a participant who is followed for the entire study period, the "Number of days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study medication, the "Number of days Should be on Therapy" is the total number of days from randomization to the date of the last dose of study medication.

For each participant, percent compliance will then be calculated using the following formula:

$$Percent\ Compliance = \frac{Number\ of\ Days\ on\ Therapy}{Number\ of\ Days\ Should\ be\ on\ Therapy} \times 100$$

Summary statistics will be provided on percent compliance by treatment group for the APaT population.

9.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary for the "Number of days on Therapy" by treatment group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutiona Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee

This study was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.4 Clinical Adjudication Committee (CAC)

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 9, as well as evaluating the presence of confounding factors.

The CAC will review clinical, virological, and histopathological data as well as the investigator's assessment for adjudicating all potential cases of CMV end-organ disease. CMV end-organ disease will be determined using the definitions in Appendix 7 (Section 10.7).

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarmen

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

Laboratory tests are detailed in Table 9.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study medication administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study medication decision or response evaluation, the results must be entered into the CRF.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Laboratory Assessments

	Laboratory Assessments	Parameters			
Central Laboratory	Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
		Albumin	Bicarbonate	Chloride	Phosphorous
		Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
		Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	
	Other Tests	• CMV DNA Sequence Analysis to be performed only in participants who have both a clinically significant CMV infection and detectable CMV DNA • CMV DNA PCR • QuantiFERON-CMV			
	Tests Performed at Screening	• Coagulation: PT/INR (using central laboratory at Screening; local laboratory testing to be used at other visits) • Creatinine Clearance (calculated using the Cockcroft-Gault equation for participants)			
Central or Local Laboratory	Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, and microscopic examination			
	Tests Performed at Screening	• Serum β human chorionic gonadotropin (β hCG) pregnancy test (for WOCBP) • Serology: HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody • HCV RNA PCR: to be done only in participants who test positive for HCV antibody			

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. The central laboratory based QuantiFERON-CMV assay results will not be shared with the respective site investigators.

Table 10 summarizes the approximate blood volumes collected by study visit and sample types.

Table 10 Approximate Blood/Tissue Volumes Drawn/Collected by Study Visit and by Sample Types

Study Period		**Treatment Period**								**Follow-up**								CMVi or Early D/C [a]
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Post-transplant (TP) Week	**SCR**	**14 (D1)**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**44**	**48**	
Blood Parameter																		
Hematology	2	2	2	2	2	2	2	2	2	2								2
Chemistry	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5								3.5
Coagulation PT/INR	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5									4.5
Serum (β-hCG) (WOCBP only)	3.5																	
HIV, Hepatitis B and C screen [b]	16																	
CMV DNA PCR [c]	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
QuantiFERON-CMV assay	3								3								3	3
CMV DNA sequence analysis [d]																		10
Expected Total (mL)	38.5	16	16	16	16	16	16	16	19	11.5	6	6	6	6	6	6	9	29

β-hCG = β-Human Chorionic Gonadotropin; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; D = day; FU = follow-up; HIV = human immunodeficiency virus; HSCT = hematopoietic stem cell transplant; IV = intravenous; LET = letermovir; PCR = polymerase chain reaction; PET = pre-emptive therapy; SCR = screening; TP = Transplant; WOCBP = woman of childbearing potential.

a. The visit will be a CMV Infection Visit for all participants who meet the endpoint of CS-CMVi (defined as the occurrence of CMV disease or the initiation of PET) through Week 48 post-transplant. The visit can also be an Early Discontinuation Visit for those participants who are prematurely discontinued from the trial up to Week 48 post-transplant. All procedures should be performed at this visit immediately prior to the initiation of treatment of CMV diseases or initiation of PET (ie, on the day anti-CMV therapy is initiated). Most importantly, a plasma sample for CMV PCR testing at the central laboratory should be collected at this visit.

b. If not documented within the previous 6 months. If hepatitis C virus antibody is positive, RNA PCR results should be provided.

c. Protocol-specified CMV DNA testing will be performed by the central laboratory using the Roche COBAS® AmpliPrep/COBAS TaqMan® [CAP/CTM] System.

d. To be performed only in participants with clinically significant CMV infection; For participants with clinically significant CMV infection, a sample for CMV DNA sequence analysis for LET resistance should be collected at the CMVi visit **and a second, confirmatory sample should be collected at the next scheduled visit** following the CMVi visit

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.7 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:

  - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship:

  - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
- Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to start contraception when initiating sexual activity and they agree to use 1 of the contraception methods described in Table 11 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 11 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen-containing) hormonal contraception [b,c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b,c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only contraceptive implant [b,c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [b] If locally required, in accordance with Clinical Trial Facilitation Group guidelines [Heads of Medicines Agencies 2014], acceptable hormonal contraceptives are limited to those which inhibit ovulation.

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of study medication, additional pregnancy testing will be performed at monthly intervals during the treatment period, for participants who complete the treatment period, at the CMV disease/early discontinuation visit, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6 Appendix 6: Country-specific Requirements

Not applicable.

10.7 Appendix 7 Definition of CMV Disease in Hematopoietic Stem Cell Transplant (HSCT) Recipients

CMV Disease Type	Probable	Proven	Notes
Pneumonia	Signs and/or symptoms of pneumonia **AND** Detection of CMV by viral isolation, rapid culture of BAL fluid, or the quantitation of CMV DNA in BAL fluid	Signs and/or symptoms of pulmonary disease **AND** Detection of CMV in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques	• PCR may be too sensitive, so detection of CMV by PCR alone is insufficient for the diagnosis of CMV pneumonia. • Superinfection or coinfection with other pathogens may occur and should be noted when present.
GI Disease	Symptoms of upper and/or lower GI disease **AND** Evidence of CMV in tissue but without the requirement for macroscopic mucosal lesions	Symptoms of upper and/or lower GI disease **AND** Macroscopic mucosal lesions **AND** Detection of CMV in GI tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization	• Detection of CMV by PCR alone is insufficient for the diagnosis of CMV GI disease.
Hepatitis	N/A	Abnormal liver function tests **AND** CMV documented in tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques **AND** Absence of other documented cause of hepatitis	• Detection of CMV by PCR alone is insufficient as it may represent transient DNAemia. Hence, PCR is insufficient to diagnose CMV hepatitis. • Documentation of CMV in liver biopsy specimen (ie, by culture, histopathology, immunohistochemical analysis or *in situ* hybridization) is needed. • Coinfection with other pathogens like HCV may be present without excluding the diagnosis of CMV hepatitis.

CMV Disease Type	Probable	Proven	Notes
Encephalitis/ ventriculitis	CNS symptoms **AND** Abnormal imaging results or evidence of encephalitis on electroencephalography **AND** Detection of CMV in CSF without visible contamination of blood	CNS symptoms **AND** Detection of CMV in CNS tissue by virus isolation, rapid culture, immunohistochemistry, *in situ* hybridization, or (preferably) quantitative PCR	N/A
Retinitis	N/A	Lesions typical of CMV retinitis confirmed by an ophthalmologist.	N/A
Nephritis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or *in situ* hybridization in a kidney allograft biopsy specimen obtained from a patient with renal dysfunction **AND** Identification of histologic features of CMV infection	• Detection of CMV in urine by PCR or culture is insufficient for the diagnosis of CMV nephritis.
Cystitis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or *in situ* hybridization in a bladder biopsy specimen obtained from a patient with cystitis **AND** Identification of conventional histologic features of CMV infection	• Detection of CMV in urine by PCR or culture is insufficient for the diagnosis of CMV cystitis.
Myocarditis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or *in situ* hybridization in a heart biopsy specimen obtained from a patient with myocarditis **AND** Identification of conventional histologic features of CMV infection	N/A

CMV Disease Type	Probable	Proven	Notes
Pancreatitis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or *in situ* hybridization in a pancreatic biopsy specimen obtained from a patient with pancreatitis AND Identification of conventional histologic features of CMV infection	N/A
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAL = bronchoalveolar lavage; CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; GI = gastrointestinal; HCV = hepatitis C virus; N/A = not applicable; PCR = polymerase chain reaction; ULN = upper limit of normal			

10.8 Appendix 8 Child-Pugh Classification for Severity of Liver Disease

	Scoring by Anomaly		
Signs or symptom	**1 point**	**2 points**	**3 points**
Hepatic encephalopathy[1]	absent	Grade 1 or Grade 2	Grade 3 or Grade 4
Ascites	absent	mild	moderate
Bilirubin (µmol/L)	< 2 mg/dL	2 – 3 mg/dL	> 3 mg/dL
Albumin (g/dL)	> 3.5 g/dL	2.8 – 3.5 g/dL	< 2.8 g/dL
Prothrombin time (INR)	< 1.7	1.7 – 2.3	> 2.3

[1]Hepatic encephalopathy grading:
Grade 1: Altered mood/confusion
Grade 2: Inappropriate behavior, impending stupor, somnolence
Grade 3: Markedly confused, stuporous but arousable
Grade 4: Comatose/unresponsive

Child-Pugh Score Interpretation	
5 – 6 points	Child-Pugh stage A (mild hepatic insufficiency)
7 – 9 points	Child-Pugh stage B (moderate hepatic insufficiency*)
≥10 points	Child-Pugh stage C (severe hepatic insufficiency)

*If hypoalbuminemia is the only abnormality noted, the participant will need to have a score of ≥7 to qualify for moderate hepatic insufficiency for this study.

Note: Central laboratory test results will be used to determine Child-Pugh score at the Screening Visit. Thereafter, local laboratory test results will be used for Child-Pugh scoring.

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
BDS	blood drug screen
CAC	Clinical Adjudication Committee
CMV	cytomegalovirus
CNS	central nervous system
CRF	Case Report Form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DEHP	diethylhexyl phthalate
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
EDC	electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GVHD	graft-versus-host disease
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MTD	maximum tolerated dose
NA	Not Applicable
NDA	New Drug Application
NOAEL	no observed adverse effect level
PCR	polymerase chain reaction
PES	polyethersulfone
PET	preemptive therapy
PK	pharmacokinetic
PT/INR	prothrombin time / international normalized ratio
QP2	department of quantitative pharmacology and pharmacometrics
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
siDMC	Standing Internal Data Monitoring Committee

Abbreviation	Expanded Term
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
UDS	urine drug screen
WOCBP	woman/women of childbearing potential

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