Official Protocol Title:	A Phase 3, Open label, Single-Arm Clinical Trial to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) for the Prevention of Clinically Significant Cytomegalovirus (CMV) Infection in Chinese Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients
NCT number:	NCT05763823
Document Date:	24-Jan-2023

TITLE PAGE

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Protocol Title: A Phase 3, Open label, Single-Arm Clinical Trial to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) for the Prevention of Clinically Significant Cytomegalovirus (CMV) Infection in Chinese Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients

Protocol Number: 045-01

Compound Number: MK-8228

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	Not Applicable
EU CT	Not Applicable
EudraCT	Not Applicable
JAPIC-CT	Not Applicable
WHO	Not Applicable
UTN	Not Applicable
IND	Not Applicable

Approval Date: 24 January 2023

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 1	24-JAN-2023	To remove the CMV resistant testing due to operational considerations.
Original Protocol	03-AUG-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

To remove the CMV resistant testing due to operational considerations.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
1.3 Schedule of Activities 8.2.3 CMV Disease Assessment 8.2.4 CMV DNA Resistance Analysis 10.2 Appendix 2: Clinical Laboratory Tests	Removed the CMV resistant testing.	This change was made to address operational considerations. The rationale is further supported by new data, considering that the resistance pattern of CMV has been characterized in other studies.
Other Changes in Amendment		
1.1 Synopsis 6.1 Study Intervention(s) Administered	The oral and IV infusion formulations of letermovir are presented in separate rows.	To ensure the clarity of IMP dose formulations and route of administration.
1.1 Synopsis 3 Hypotheses, Objectives, and Endpoints	Switched the order of the following secondary endpoints: “CMV disease” comes before “initiation of PET for document CMV viremia”.	The order of secondary endpoints should be consistent with the definition of clinically significant CMV infection.
1.3 Schedule of Activities	Clarified the definition of Week No. and Visit Window. Deleted the row of FU Week No..	To ensure clarity of the SoA and accurate conduct of the trial.

Section Number and Name	Description of Change	Brief Rationale
10.2 Appendix 2 Clinical Laboratory Tests	Removed pH, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase tests from the routine urinalysis. Routine Urinalysis will include specific gravity, glucose, protein, blood, and microscopic examination (if blood or protein is abnormal).	Clinical laboratory analysis method changes.
Throughout the document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Open label, Single-Arm Clinical Trial to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) for the Prevention of Clinically Significant Cytomegalovirus (CMV) Infection in Chinese Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients

Short Title: MK-8228 (Letermovir) for Prevention of CMV infection in Chinese HSCT Recipients

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

There are no hypotheses to be tested in this study.

The following objectives and endpoints will be evaluated in Chinese adult CMV-seropositive allogeneic HSCT recipients:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of letermovir in the prevention of clinically significant CMV infection, as measured by the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant.	Clinically significant CMV infection, defined as onset of CMV disease and/or initiation of PET for documented CMV viremia
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of letermovir based on the proportion of participants with AEs.	• AEs • AEs resulting in study medication discontinuation
To evaluate the efficacy of letermovir in the prevention of clinically significant CMV infection, as measured by the proportion of participants with clinically significant CMV infection through Week 14 (~100 days) post-transplant.	Clinically significant CMV infection, defined as onset of CMV disease and/or initiation of PET for documented CMV viremia

To evaluate the efficacy of letermovir in the prevention of clinically significant CMV infection, as measured by: • proportion of participants with CMV disease through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant. • proportion of participants with initiation of PET for documented CMV viremia through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant. • proportion of participants with all-cause mortality through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant.	• CMV disease • Initiation of PET for document CMV viremia • All-cause mortality

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Cytomegalovirus prophylaxis
Population	Adult Chinese CMV-seropositive allogeneic HSCT recipients
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 23 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 120 participants will be allocated.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Letermovir	Letermovir	240 mg	240 mg (for participants on CsA) OR 480 mg (for participants not on CsA)	Oral	Through Week 14 (~100 days) post-transplant	Test Product
Letermovir	Letermovir	240 mg	240 mg (for participants on CsA) OR 480 mg (for participants not on CsA)	IV Infusion	Through Week 14 (~100 days) post-transplant	Test Product

Note: This is a single-arm study. Both oral (tablet) and IV formulations of letermovir will be available for study intervention. Participants will be initiated with the oral formulation of study intervention provided they are able to swallow and do not have a condition that may interfere with the absorption of the tablets. For participants who cannot swallow and/or have a condition that may interfere with the absorption of the oral formulation, study intervention can be initiated with or switched to the IV formulation. The IV formulation should be switched to oral study intervention (i.e., at the next planned dose) as soon as such participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves.

Total Number of Intervention Groups/Arms	1 (single-arm study)
Duration of Participation	Each participant will participate in the study for approximately 25 weeks from the time the participant signs the informed consent form (ICF) through the final contact. Participants can be screened from up to 15 days prior to receipt of HSCT to 28 days post-HSCT. Allocation of study intervention can be initiated as early as the day of transplant but must be completed within 28 days post-transplant. All participants will receive study treatment until Week 14 (~100 days) post-transplant. After the end of study treatment, each participant will be followed until Week 24 post-transplant.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	Yes

Study governance considerations are outlined in Appendix 1.

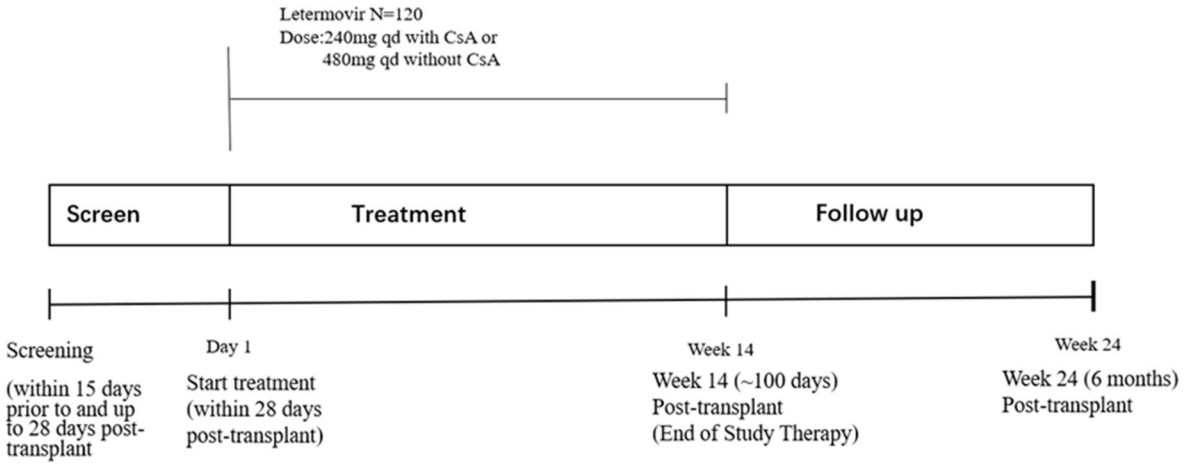
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



* For participants who cannot tolerate swallowing and/or develop a condition that may interfere with the absorption of the oral formulation of letermovir, study intervention can be initiated/switched to the IV formulation of letermovir. The IV formulation should be switched to oral study therapy (i.e., at the next planned dose) as soon as such participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves.

CsA = cyclosporin A

1.3 Schedule of Activities

Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
Administrative Procedures																							
Informed Consent	X																						
Inclusion/ Exclusion Criteria	X	X																					Confirm inclusion/exclusion prior to 1st dose of study intervention.
Participant Identification Card	X																						
Medical History	X																						
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Intervention Allocation		X																					
HSCT Details Review		X																					
Study Medication Diary Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X	
Clinical Procedures/ Assessments																							
Full Physical Examination	X	X																					

Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
Targeted Physical Examination			Performed only when clinically indicated																				
Weight	X															X						X	
Height	X																						
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	
12-Lead Electrocardiogram	X															X						X	Read locally. Values collected within 1 week prior to screening are acceptable for Visit 1. ECG will be obtained after participants resting for at least 10 minutes.
Child-Pugh Score	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X	Refer to 8.3.4 and Appendix 9.

Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
Participant Confirmation of Birth Control	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	For male participants, no contraception measures are needed during letermovir treatment. For female participants of child-bearing potential, acceptable methods of contraception should be used from the time of consent through 28 days after the last dose of study intervention.

Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
Adverse Events Monitoring[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All AEs will be reported through 14 days after last dose of study medication. Thereafter, only SAEs will be reported through Week 24 post-transplant (see Section 8.4)
Laboratory Procedures/ Assessments																							
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	Screening values from the participant's chart within 5 days prior to allocation for required chemistry, hematology, coagulation, and urinalysis tests are acceptable. Refer to Section8.3.6 for further details regarding the laboratory safety tests.

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Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	
Coagulation INR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X	
Urinalysis	X	X														X						X	
Serum β-hCG in women of childbearing potential	X																						
Urine Pregnancy Test in women of childbearing potential		X				X				X						X						X	Performed locally; serum pregnancy test must be performed to confirm a positive urine test result.
HIV/Hepatitis B, C Screen	X																						Screening values from the participant's chart within 90 days prior to allocation for required tests are acceptable.

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Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
CMV Procedures/ Assessments																							
CMV DNA PCR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	CMV DNA will be tested weekly during the screening period (time between Screening and Day 1) by central lab after establishing absence of CMV viremia.
CMV Serology (IgG)	X																						Perform locally per SOC at the site. This testing is not required if a previous documented positive IgG testing result within 1 year before HSCT is available.

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Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
CMV Disease Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All clinical signs and symptoms of CMV disease and review of relevant laboratory parameters
Survival Assessment																X					X		
Study Intervention Administration																							
Letermovir dispensing (oral formulation)		X		X		X		X		X		X		X									For participants receiving the oral formulation of study intervention, letermovir tablets will be dispensed on Day 1 and every 2 weeks starting from Week 2. Contact IRT at all dispensing visits.

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Study Period	Screen	Treatment (W1)		Treatment (W2 to W14 post-transplant)													Post-treatment FU (W15 to W24 post-transplant)						
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Notes
Week No.	SCR[a]	D1[b]	D7	2	3	4	5	6	7	8	9	10c	11c	12c	13c	EoT 14[c]	16	18	20	22	24	CMV Infection or Early Discontinuation Visit[d,e]	Week No. of Treatment period is relative to the day of first dose of study intervention.
Visit Window (Days)			±2	±3													±4						±3 days every 2 week during treatment period to align with drug dispensation.
Letermovir administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							IV formulation available for participants unable to tolerate swallowing and/or have a condition that may interfere with the absorption of oral formulation.
Study medication reconciliation and diary review			X	X	X	X	X	X	X	X	X	X	X	X	X	X						X	Diary should be completed for participants receiving the oral formulation of study intervention only.

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β-HCG = β-Human Chorionic Gonadotropin CMV = cytomegalovirus; D = Day; DNA = deoxyribonucleic acid; EoT = End-of-Treatment; FU = follow up; HIV = human immunodeficiency virus; HSCT = hematopoietic stem cell transplant; PCR = polymerase chain reaction; SCR = screening; W = week.

a. Participants may be screened during a period starting from 15 days prior to transplantation through 28 days post-transplant. The screening test results must be available within 5 days prior to the planned allocation (start of study intervention) day. The following tests are to be performed within 5 days prior to allocation and results must be available prior to allocation: coagulation (INR), serum AST, ALT, and total bilirubin; creatinine clearance. For CMV DNA PCR, results of the assay done at a local laboratory will be acceptable for initial screening purposes.
b. Allocation (start of study intervention) day is Day 1. On the day of allocation, eligibility for enrollment into the study should be confirmed (including confirmation that HSCT has taken place) prior to start of study intervention. At that time, participants should have **NO** documented CMV viremia, as confirmed by CMV DNA PCR assay at the central laboratory in a plasma sample collected within 5 days prior to allocation. In addition, creatinine clearance and liver function test results within 5 days prior to allocation should also be available and within the range allowable in this study as outlined in Section 5.2 (Participant Exclusion Criteria). Study intervention may begin as early as the day of transplant and no later than 28 days post-transplant. Study intervention will continue through Week 14 (~100 days) post-transplant. Day 1 procedures/assessments must be performed prior to initiation of study intervention.
c. End of Study Therapy Visit may occur on Week 10, 11, 12, 13, or 14 depending on when study therapy was started during the 28-day post-transplant window. For example, if study therapy was started on the day of transplant, the End of Study Therapy Visit would be the Week 14 Visit (which corresponds to Week 14 post-transplant). If study therapy was started 28 days post-transplant, the End of Study Therapy Visit would be the Week 10 Visit (which corresponds to Week 14 post-transplant). Any per protocol procedure listed under the Week 14 Visit should be conducted at the true End of Study Therapy Visit (at Week 10, 11, 12, 13, or 14 post-transplant, depending on when study therapy was started).
d. The visit will be a CMV Infection Visit for all participants who discontinue study intervention due to clinically significant CMV infection defined as the occurrence of CMV disease or the initiation of PET, or for participants who are either diagnosed with CMV disease or require initiation of PET after study intervention completion during the follow-up period (through Week 24 post-transplant). All procedures should be performed at this visit **immediately prior to** the initiation of treatment of CMV diseases or initiation of PET (i.e., on the day anti-CMV therapy is initiated). Most importantly, a confirmatory plasma sample for CMV PCR testing at the central laboratory should be collected at this visit. Refer to Section 8.2.1 and Section 8.10.4 for detailed requirements.
e. The visit will be an Early Discontinuation Visit for those participants who are prematurely discontinued from the trial up to Week 24 post-transplant.
f. Adverse event (AE) monitoring prior to allocation (Day 1) is limited to AEs resulting from protocol-related procedures or interventions, those resulting in death, and those resulting in a participant not being allocated. After initiating study intervention, all AEs should be collected from Day 1 through 14 days after last dose of study medication. Thereafter, only serious adverse events (SAEs) will be collected through Week 24 post-transplant in all participants.

2 INTRODUCTION

Letermovir (also known as MK-8228) is an inhibitor of the CMV viral terminase complex. As of July 2022, letermovir has been approved for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients (R+) of an allogeneic HSCT in several markets, including US, EU, Japan, Korea, Singapore, China Taiwan, and China Hong Kong.

Letermovir tablet and IV formulations received approval in China for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients (R+) of an allogeneic HSCT on 31 December 2021 and 10 May 2022, respectively.

The efficacy and safety of letermovir for CMV prophylaxis in adult CMV-seropositive recipients (R+) of an allogeneic HSCT has been established in the global pivotal double-blinded, placebo-controlled Phase 3 trial (P001). However, as no Chinese participants were included in Study P001, the P045 study will be conducted to evaluate the efficacy and safety of letermovir for the prevention of clinically significant CMV infection in Chinese adult, CMV-seropositive allogeneic HSCT recipients. Of note, in this study, “Chinese participants” refer to participants who live in mainland China and who are ethically Chinese.

2.1 Study Rationale

CMV continues to be an important complication after allogeneic HSCT [Ljungman, P., et al 2002] [Boeckh, M. 2011]. The clinical effects of CMV can be divided into direct and indirect effects [Ljungman, P., et al 2002] [Boeckh, M. 2011]. The direct effects which have been extensively described include the spectrum of CMV disease (ie, end-organ manifestation). CMV gastroenteritis is the most common clinical presentation in this population. While CMV pneumonia is the most serious manifestation, it has become relatively infrequent with current preventive strategies for CMV disease in HSCT recipients [Boeckh, M. 2011] [Boeckh, M. and Geballe, A. P. 2011]. Other rare manifestations of CMV disease include hepatitis, retinitis, and encephalitis [Ljungman, P., et al 2002] [Boeckh, M. 2011]. The indirect effects of CMV include its immunosuppressive effects, which can lead to an increased risk of systemic bacterial and invasive fungal disease as well as acute and chronic GVHD [Boeckh, M. 2011] [Boeckh, M. and Nichols, W. G. 2004].

Between 65% and 80% of adult HSCT recipients have evidence of prior CMV seropositivity globally and are therefore at risk for CMV reactivation (also referred to as CMV infection) and CMV disease post-transplantation [Ljungman, P. 2014] [Razonable, R. R. 2005] [Zhou, W., et al 2009]. In China, CMV seropositive (R+) patients account for about 95% of allogeneic HSCT patients, which is higher than the Western population [Xuan, L., et al 2012]. Among R+ HSCT recipients, approximately 80% of recipients develop CMV infection and 20% to 35% progress to CMV disease without preventive measures [Boeckh, M. 2011] [Boeckh, M. and Geballe, A. P. 2011] [Boeckh, M. and Nichols, W. G. 2004]. The highest risk period for developing CMV infection (ie, virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen) is during the first 100 days post-transplant [Boeckh, M. 2011] [Boeckh, M. and Geballe, A. P. 2011] [Boeckh, M. and Nichols, W. G. 2004] [Nakamae, H., et al 2009].

Recipients with CMV seropositivity remain associated with poor outcomes especially in high risk HSCT patients, ie, unrelated donors or cord blood recipients [Boeckh, M. 2011] [Nakamae, H., et al 2009]. The source of stem cells and the conditioning regimens may also influence both the time to reactivation as well as the severity of disease [Nakamae, H., et al 2009] [Marty, F. M., et al 2011] [Sauter, C., et al 2011]. There are currently 2 approaches to prevent CMV disease in HSCT recipients: 1) prophylaxis with antivirals, and 2) pre-emptive therapy (PET), the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV viremia is detected [Ljungman, P., et al 2002]. Prior to the availability of letermovir, all available anti-CMV agents were associated with significant toxicity, and resistance and cross-resistance across these antiviral agents is increasingly being reported. Thus, antivirals were not routinely used for the prophylaxis of CMV infection in HSCT patients, and there was a clear need for safe and well-tolerated drugs with novel mechanisms of action against CMV that can be used for prophylaxis in HSCT patients.

Letermovir is a novel anti-CMV agent that has been shown to be generally well tolerated in 32 Phase 1 trials, 2 Phase 2 clinical trials (P019 and P020, respectively), and a single, pivotal Phase 3 efficacy and safety trial (P001). The results of the pivotal global Phase 3 trial (P001) establish the efficacy and safety of letermovir for CMV prophylaxis in adult CMV-seropositive recipients (R+) of an allogeneic HSCT. In this randomized, placebo-controlled Phase 3 study, letermovir prophylaxis when started within 28 days posttransplant and continued until Week 14 (~100 days) posttransplant effectively prevented clinically significant CMV viremia through Week 24 posttransplant. At Week 14 posttransplant (end of study treatment), 19.1% participants on letermovir developed clinically significant CMV infection compared to 50% participants on placebo. Letermovir was well-tolerated with no evidence of myelotoxicity.

This post-approval commitment study is planned to evaluate the efficacy and safety of letermovir in preventing clinically significant CMV infection in Chinese adult CMV seropositive allogeneic HSCT recipients.

2.2 Background

Refer to the IB for detailed background information on letermovir.

2.2.1 Pharmaceutical and Therapeutic Background

Prior to the availability of letermovir, there was no oral anti-CMV drug approved for prophylaxis of CMV disease in HSCT patients. Use of GCV, VGCV, and foscarnet are limited by their toxicity profiles (prolonged myelosuppression, renal toxicity, and electrolyte abnormalities, respectively) [Boeckh, M. 2009]. Acyclovir and valacyclovir have limited efficacy against the virus [Boeckh, M. 2011] [Pollack, M., et al 2011] [Biron, K. K. 2006]. Additionally, there is increasing emergence of resistance and cross-resistance to currently available antiviral agents [Boeckh, M. 2009] [Lurain, N. S. and Chou, S. 2010]. Thus, there is an urgent need for newer efficacious agents with better tolerability and novel mechanisms of action for CMV prophylaxis in HSCT patients.

Letermovir, which belongs to a new class of anti-CMV agents, has a novel mechanism of action. It has demonstrated potent, selective, and reversible inhibition of CMV activity in preclinical studies in vitro and efficacy against the virus in vivo [Lurain, N. S. and Chou, S. 2010] [Lischka, P., et al 2010]. It inhibits the viral terminase complex (UL56/UL89), an enzyme that plays an important role in cleavage of viral DNA into unit-length genome and packaging it into procapsids [Lischka, P., et al 2010] [Goldner, T., et al 2011].

While drug resistance remains rare, most resistance arises during treatment with GCV (or VGCV) as they are used in ~90% of patients as first-line agents. Drug resistance is usually seen after treatment with these antiviral agents for duration of weeks to months [Boeckh, M. 2009]. GCV and VGCV undergo intracellular phosphorylation by a viral kinase, which is encoded by the CMV gene UL97 during infection and the majority of resistance mutations with use of these therapies map to this gene [Lurain, N. S. and Chou, S. 2010]. It has been postulated that UL97 mutations arise first and confer moderate resistance to GCV (or VGCV) but not to other CMV antivirals, such as cidofovir or foscarnet. However, all current anti-CMV agents (with the exception of letermovir) act through the viral polymerase (UL54) and resistance mapping to this gene product leads to cross-resistance among all available agents [Lurain, N. S. and Chou, S. 2010]. To date, no cross-resistance has been demonstrated between letermovir and GCV, foscarnet, cidofovir, or acyclovir [Kaul, D. R., et al 2011].

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

There are two ongoing clinical studies involving letermovir for HSCT patients: 1) P040, a Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of letermovir prophylaxis when extended from 100 days to 200 days post-transplant in CMV R+ at high risk for CMV infection and/or disease after ~100 days post-transplant of an allogenic HSCT; 2) P030, a Phase 2b open-label, single-arm study to evaluate pharmacokinetics, efficacy, safety and tolerability of letermovir in pediatric participants from birth to less than 18 years of age. Additionally, there are 2 ongoing clinical studies involving letermovir for adult solid organ transplant patients:1) P002, a Phase 3 randomized, multi-site, double-blind active comparator trial to evaluate the efficacy and safety of letermovir versus VGCV in adult kidney transplant recipients; 2) P042, a Phase 3, open-label, single-arm study to evaluate the safety, efficacy and pharmacokinetics of letermovir for the prevention in adult Japanese kidney transplant recipients.

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.

Efficacy data from the global Phase 2 and 3 studies have demonstrated that letermovir is highly efficacious in preventing CMV infection and disease in HSCT patients [Turner, N., et al 2019] [Marty, F. M., et al 2017]. Safety data (cut-off date: 1 May 2022) from 1,759 participants exposed to letermovir across the clinical program indicated that overall letermovir has a favorable safety profile that is generally similar to placebo. The effect of race on letermovir exposure is not considered to be clinically relevant, and no dose adjustment is required. Based on available clinical data from non-Chinese patients, the study participants may potentially benefit from prevention of clinically significant CMV infection.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There are no hypotheses to be tested in this study.

The following objectives and endpoints will be evaluated in Chinese adult CMV-seropositive allogeneic HSCT recipients:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of letermovir in the prevention of clinically significant CMV infection, as measured by the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant.	Clinically significant CMV infection, defined as onset of CMV disease and/or initiation of PET for documented CMV viremia
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of letermovir based on the proportion of participants with AEs.	• AEs • AEs resulting in study medication discontinuation
To evaluate the efficacy of letermovir in the prevention of clinically significant CMV infection, as measured by the proportion of participants with clinically significant CMV infection through Week 14 (~100 days) post-transplant.	Clinically significant CMV infection, defined as onset of CMV disease and/or initiation of PET for documented CMV viremia
To evaluate the efficacy of letermovir in the prevention of clinically significant CMV infection, as measured by: • proportion of participants with CMV disease through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant. • proportion of participants with initiation of PET for documented CMV viremia through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant. • proportion of participants with all-cause mortality through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant.	• CMV disease • Initiation of PET for document CMV viremia • All-cause mortality

4 STUDY DESIGN

4.1 Overall Design

This is an open label, single-arm, multi-site trial of letermovir in the prevention of clinically significant CMV infection in Chinese adult, CMV-seropositive allogeneic HSCT recipients. Clinically significant CMV infection is defined as the occurrence of either one of the following outcomes:

- Onset of CMV end-organ disease, or
- Initiation of anti-CMV PET based on documented CMV viremia (as measured by the central laboratory) and the clinical condition of the participant.

Approximately 120 eligible HSCT recipients will be allocated to receive letermovir at any time from the day of transplant until 28 days post-transplant. Both oral (tablet) and IV formulations of letermovir will be available for study intervention. Participants will be initiated with the oral (tablet) formulation of study intervention provided they are able to swallow and do not have a condition (e.g., vomiting, diarrhea, or a malabsorptive condition) that may interfere with the absorption of the tablets. For participants who cannot swallow and/or have a condition that may interfere with the absorption of the oral formulation (e.g., vomiting, diarrhea, or a malabsorptive condition), study intervention can be initiated with or switched to the IV formulation. The IV formulation should be switched to oral study intervention (i.e., at the next planned dose) as soon as such participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves.

The dose of letermovir will either be 240 mg QD, for participants receiving concomitant CsA, or 480 mg QD, if the participant is not on CsA. As CsA has been shown to increase letermovir exposure, the dose of letermovir must be adjusted for participants taking CsA (concomitant use of other immunosuppressive agents like tacrolimus does not require this adjustment).

Participants will be grouped by the following risk categories for CMV reactivation and/or disease to observe the efficacy of letermovir based on risk category (see Section 4.2.1.1), as participants in the high-risk category are more likely to develop clinically significant CMV infection than those in the low-risk group.

High risk: Participants meeting one or more of the following criteria at the time of allocation:

1. HLA-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR,
2. Haploidentical donor,
3. Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1,
4. Use of umbilical cord blood as stem cell source,

5. Use of ex vivo T-cell-depleted grafts (including ex vivo use of alemtuzumab [Campath™]),
6. Grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).

Low risk: All participants not meeting definition of high risk.

Participants must have documented seropositivity for CMV (recipient CMV IgG seropositivity [R+]) at screening or within one year prior to transplantation to be eligible for the study. Donor CMV serostatus may either be positive (D+) or negative (D−). Screening of potential eligible participants may begin within 15 days prior to transplantation. Screening may also occur after the transplant, but allocation (start of study intervention) must occur no later than 28 days post-transplant. Participants will have plasma samples tested for CMV viremia using the CMV DNA PCR assay, conducted by the central laboratory (Note: for initial screening purposes, results of the assay done at a local laboratory will be acceptable.) After establishing absence of CMV viremia, participants will be tested once a week by the central laboratory using the CMV DNA PCR assay until allocation in order to minimize enrollment of those with active CMV replication in the study. Note: the screening test results must be available within 5 days prior to the planned allocation date. Any participant who tests positive for CMV viremia (as documented by central laboratory results) prior to allocation at any time point will be excluded from the study, even if subsequent tests are negative for CMV viremia. Once allocated, CMV viremia will be monitored at the time intervals detailed in the Schedule of Activities (Section 1.3).

Study intervention (with letermovir) may begin as early as the day of transplant and no later than 28 days post-transplant. Study intervention will continue through Week 14 (~100 days) post-transplant with the primary intent of preventing clinically significant CMV infection. On the day of allocation, eligibility for enrollment into the study should be confirmed (including confirmation that HSCT has taken place). At that time, participants should have no documented CMV viremia (as confirmed by the central laboratory) from a plasma sample collected within 5 days prior to allocation. In addition, creatinine clearance and liver function test values from testing performed within 5 days prior to allocation should also be available and within the range allowable in this study as outlined in Section 5.2 (Participant Exclusion Criteria).

Once enrolled in the study, participants will have study visits scheduled at weekly intervals during the treatment period which will be through Week 14 (~100 days) post-transplant. For participants receiving the oral formulation of study intervention, letermovir tablets will be dispensed on Day 1 and every 2 weeks starting from Week 2. Visit schedules must align the weekly visits with the drug dispensation every 2 weeks. Thereafter, participants will be followed through Week 24 (~6 months) post-transplant. At all study visits through Week 24 post-transplant, plasma samples will be collected for CMV DNA PCR testing (for testing by central laboratory) and the investigator must assess the participant to determine if the participant meets one of the criteria for clinically significant CMV infection (as defined above).

Participants who are enrolled and start study treatment (letermovir) should not be discontinued from the study if the Day 1 CMV DNA PCR results are subsequently positive.

In the event test results from the central laboratory are not available within the timeframe the investigator wishes to initiate anti-CMV therapy, the investigator may use local laboratory test (CMV DNA PCR) results in order to make the decision. However, plasma samples for CMV DNA PCR testing must also be sent to the central laboratory on the day anti-CMV agents are initiated for PET or for treatment of CMV disease. The local laboratory result must also be reported in such instances.

For participants who develop clinically significant CMV infection during the study treatment period (up to Week 14 post-transplant): When the investigator intends to initiate either treatment for CMV disease or PET, the participant should have **a CMV Infection Visit**. It is very important to ensure that all procedures, as outlined in the Schedule of Activities (Section 1.3), are performed at the CMV Infection Visit **immediately prior to** the initiation of treatment of CMV diseases or initiation of PET (i.e., on the day anti-CMV therapy is initiated). Most importantly, a confirmatory plasma sample for CMV PCR testing at the central laboratory should be collected at this visit. Thereafter, the participant should be discontinued from study intervention and treated according to the local standard of care (outside the context of the study). Such participants will, however, continue to be followed in the study (despite discontinuing study intervention and initiating anti-CMV therapy) and complete all remaining study visits (including all subsequent treatment period visits). At such subsequent visits, all procedures specified in the Schedule of Activities should be completed with the exception of study intervention administration and study medication diary review.

Note on reinitiation of study intervention: There may be instances where confirmatory central lab test results for CMV DNA PCR obtained on the day of PET initiation may be negative (i.e., CMV DNA not detected) and the investigator may wish to discontinue PET. The decision to stop PET in the event of a negative (CMV not detectable) confirmatory central laboratory result collected on the day of PET initiation resides with the investigator caring for the participant. Therefore, in the event the confirmatory CMV DNA sample at PET initiation is negative for CMV viremia, the Sponsor will allow for letermovir to be restarted at the investigator's discretion, once PET is discontinued. In such instances, study intervention should be restarted within 7 days from the date on which study intervention is stopped. It is important to note that the status of the participant's study intervention in IVRS should NOT be changed until the CMV DNA PCR result is confirmed and the investigator is certain that study intervention will be permanently discontinued.

For participants with clinically significant CMV infection during the post-treatment [follow-up] period (after Week 14 and through Week 24 post-transplant): When an investigator intends to initiate either treatment for CMV disease or PET, the participant should have a CMV Infection Visit. It is very important to ensure that all procedures, as outlined in the Schedule of Activities (Section 1.3), are performed at the CMV Infection Visit **immediately prior to** the initiation of treatment of CMV diseases or initiation of PET (i.e., on the day anti-CMV therapy is initiated). Most importantly, a confirmatory plasma sample for CMV PCR testing at the central laboratory should be collected at this visit. Thereafter, the participant can be treated according to the local standard of care (outside the context of

the study). Such participants will, however, continue to be followed in the study (despite initiation of anti-CMV therapy) and complete all remaining study visits). At such subsequent visits, all procedures specified in the Schedule of Activities should be completed.

Note: It is mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the **central laboratory immediately prior to** (i.e., on the day of) initiating treatment for CMV disease or PET in **ALL** instances. In the event that the confirmatory result obtained on the day of PET initiation is **NOT** available (e.g., sample is lost or mishandled by the investigator site prior to shipment, or is inadequate upon receipt at the central laboratory), local lab may be used in the interest of clinical management, but a subsequent sample must be obtained and sent to the central laboratory within 7 days after PET initiation (preferably within 48-72 hours). The participant will be considered to have met the primary efficacy endpoint if this confirmatory laboratory result is positive.

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

Participants who are discontinued from the study for any reason will not be replaced. Participants who discontinue the study early up to Week 24 post-transplant should complete an Early Discontinuation Visit.

An independent CAC will be established. Investigators will report all “probable” and “proven” cases of CMV disease using the definitions in Appendix 8. All investigator-reported diseases will be confirmed by the independent CAC. This CAC will review clinical, virologic, and histopathological data as well as the investigator’s assessments for adjudicating all potential cases of CMV end-organ disease, as defined in Appendix 8 throughout the trial. The adjudication of cases by the CAC will take precedence over the investigator’s assessment.

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

4.2 Scientific Rationale for Study Design

The P045 study is designed as a single-arm and open-label study for CMV-seropositive allogeneic HSCT recipients as a large global double-blinded placebo-controlled trial demonstrating the safety and efficacy of letermovir has previously been conducted. As letermovir is now approved for CMV prophylaxis, and no other approved anti-CMV agent is available for CMV prophylaxis in this population, it is not appropriate for this post approval study to be conducted with a placebo/active comparator.

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 through Week 24 (~6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- Onset of CMV end-organ disease

  OR

- Initiation of anti-CMV PET based on documented CMV viremia (as measured by the central laboratory) and the clinical condition of the participant. Initiation of PET in this study refers to the practice of initiating therapy with the following approved anti-CMV agents when active CMV viral replication is documented: ganciclovir, valganciclovir, foscarnet, and/or cidofovir.

Note: in this document, below terms are used interchangeably: CMV disease and CMV end-organ disease.

As detection of CMV in plasma or blood is associated with an increased risk of CMV disease [Gerna, G., et al 2011] [Lowance, D., et al 1999] [Gor, D., et al 1998] [Atkinson, C. and Emery, V. C. 2011], CMV viral DNA as a measure of CMV infection is already used routinely in China and global clinical practice to initiate and monitor PET [Boeckh, M. 2011] [Boeckh, M. 2009] [Winston, D. J., et al 2008] [Härter, G. and Michel, D. 2012] [Emery, V. C., et al 2000]. Patients with high viral loads or with cumulative high viral loads are at an increased risk of developing disease than those with lower viral loads [Härter, G. and Michel, D. 2012] [Emery, V. C., et al 2000]. However, there is no clinically validated viral load threshold for initiating pre-emptive therapy at this point in time.

In this study, CMV viremia (viral load) will be measured on plasma samples using the Roche COBAS® 6800 System, which will be performed by the central laboratory. The lower limit of quantification (LLoQ) for this assay is 34.5 IU/ml (1 IU/ml = 1.1 copy/ml). Results will be reported as:

- Not detected (<34.5 IU/mL)
- Detected, not quantifiable (<34.5 IU/mL)
- Detected (numeric value provided)

Documented viremia is defined as any detectable **(includes reporting of PCR results as "detected, not quantifiable" or "detected" with a numeric value provided)** CMV viral DNA on a confirmatory sample obtained immediately prior to (i.e., on the day of) the initiation of treatment for CMV disease or PET, as measured by the Roche COBAS® 6800 System in the central laboratory. While any detectable CMV viral DNA results in the Roche COBAS® 6800 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 strongly recommended that investigators should not initiate PET when CMV viral load is below the LLoQ, but detectable (detected, not quantifiable [<34.5 IU/mL]).

The following guidance regarding viral load thresholds for initiation of PET is being provided based on risk as defined in Section 4.1 as well as consideration of standard practice described by [Boeckh, M. 2009], which was also used in the global pivotal Phase 3 study (P001), and are as follows:

<u>During the study treatment period [through Week 14 (~100 days) post-transplant]</u>

- High risk: viral DNA ≥150 copies/mL
- Low risk: viral DNA >300 copies/mL

<u>After Week 14 (~100 days) post-transplant</u>

- High risk: viral DNA >300 copies/mL
- Low risk: viral DNA >300 copies/mL

These thresholds for initiation of PET are provided as guidance based on the participant's risk for CMV disease at baseline. However, specific thresholds for initiating PET are not mandated per protocol as a participant's risk status and clinical condition may change during the course of the trial and is best assessed by the investigator taking care of the participant.

Note: **<u>All</u>** study-related CMV DNA PCR samples must be sent to the central laboratory at the designated time points in the Schedule of Activities (Section 1.3). It is strongly recommended that investigators use quantifiable viremia levels (at levels ≥LLoQ) detected by the central laboratory to drive decisions for initiating PET. It is mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory **<u>immediately prior to</u>** (i.e., on the day of) initiating treatment for CMV disease or PET in **ALL** instances. In the event that the confirmatory result obtained on the day of PET initiation is **NOT** available (e.g., 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 7 days after PET initiation (preferably within 48-72 hours). The participant will be considered to have met the primary efficacy endpoint if this confirmatory laboratory result is positive.

In the event test results from the central laboratory are not available within the timeframe the investigator wishes to initiate anti-CMV therapy, the investigator may use positive local laboratory test (CMV DNA PCR) results in order to make the decision. However, as described above, plasma samples for CMV DNA PCR testing must also be sent to the <u>central laboratory</u> on the day anti-CMV agents are initiated for PET or for treatment of CMV disease. The local laboratory result must also be reported in such instances.

4.2.1.2 Safety Endpoints

The safety and tolerability of letermovir will be assessed by a clinical evaluation of adverse experiences and evaluation of other study parameters including vital signs, physical examination, 12-lead ECGs, and standard laboratory safety tests at appropriate time points as specified in the Schedule of Activities (Section 1.3) and Section 8.4. Adverse experiences should be graded and recorded. Participants may be asked to return for unscheduled visits for additional safety monitoring.

4.2.2 Rationale for Sample Size

This is an estimation study with no hypotheses to be tested. This study will allocate approximately 120 participants to receive letermovir and will allow estimation of the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant among participants receiving letermovir with a 95% confidence interval with a half-width of ~10 percentage points. Refer to Section 9.9.1 for detailed method of sample size calculation.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

This clinical study will evaluate:

Letermovir

- Oral/IV 480 mg QD, if given without concomitant CsA, or
- Oral/IV 240 mg QD, if given concomitantly with CsA

Rationale for Dose of Letermovir

Letermovir belongs to a new class of anti-CMV agents which have a novel mechanism of action compared to currently available drugs for the treatment of CMV infection. By inhibiting the viral terminase complex, the drug plays a key role in disrupting the normal process of cleavage and packaging of genomic viral DNA into provirions and subsequently prevents the completion of viral replication.

Letermovir has been generally safe and well tolerated in 32 Phase 1 studies in which participants received oral letermovir single doses ranging from 5 mg to 720 mg and multiple doses ranging from 40 mg QD to 720 mg BID or received IV letermovir single doses ranging from 30 mg to 960 mg and multiple doses ranging from 120 mg QD to 480 mg QD. In the Phase 2b study (Protocol 020), letermovir doses of 60 mg, 120 mg, or 240 mg or placebo, were given once daily in 131 HSCT recipients. Letermovir 240 mg QD, during an 84-day treatment period, was well tolerated with a safety profile similar to placebo. A dose response was observed. One primary endpoint, the incidence of overall failure of CMV prophylaxis, was significantly reduced in the primary efficacy analyses with both the 120 mg and 240 mg doses of letermovir (32%, p=0.014 and 29%, p=0.007, respectively) when compared to

placebo (63.6%). However, the second primary efficacy endpoint, the time to onset of overall failure of CMV prophylaxis, was significantly reduced in the 240 mg group (p=0.002), but not in the 120 mg group (p=0.126), when compared to placebo. All sensitivity analyses confirmed the statistical significance of both the primary endpoints for the 240 mg QD dose of letermovir when compared to placebo. Letermovir was generally well-tolerated at all three doses in P020.

Phase 1 studies demonstrated that co-dosing with CsA increases letermovir exposure. Further analyses using the Phase 2b study (P020) data indicated that exposure with the 240 mg QD dose of letermovir administered alone overlaps exposure levels of the 60 and 120 mg QD doses, which are associated with virologic failures. Based on the Phase 2b efficacy and safety data as well as the exposure-response data, a dose of 480 mg QD was proposed in participants who are not receiving CsA concomitantly, and 240 mg QD was proposed as the dose for participants receiving CsA concomitantly. The dose of letermovir for evaluation in the Phase 3 pivotal study was 480 mg with a dose adjustment to 240 mg when given concomitantly with CsA.

The efficacy and safety of letermovir 480 mg QD (or 240 mg QD with concomitant CsA) was demonstrated in a Phase 3, randomized, placebo-controlled study (P001) in adult CMV seropositive allogeneic HSCT recipients including Asian participants[Marty, F. M., et al 2017]. Treatment with letermovir or placebo was started as early as the day of transplant and no later than 28 days post-transplant and continued through Week 14 post-transplant; participants were followed through Week 48 post-transplant. Overall, the results showed a robust and efficacious response for letermovir compared to placebo. Letermovir was superior to placebo in the prevention of clinically significant CMV infection through Week 24 post-transplant, and the proportion of participants with clinically significant CMV infection was substantially lower in the letermovir group compared to the placebo group. All-cause mortality was substantially lower in the letermovir group compared to the placebo group through Week 24 post-transplant, with a continued trend in favor of letermovir through and Week 48 post-transplant. Letermovir was well tolerated in HSCT recipients and had a safety profile which was generally similar to placebo with no evidence of myelotoxicity, nephrotoxicity, or hepatotoxicity.

For the P045 study, the doses of letermovir that were previously used in the Phase 3 evaluation in global HSCT recipients including Asian participants will be used. The letermovir doses that have shown to be effective in the global HSCT recipient population is anticipated to be effective in the Chinese population.

The IV formulation of letermovir contains the excipient hydroxypropyl betadex. There is a possibility that in participants with renal impairment, worsening of renal function and other untoward effects might occur due to accumulation of the excipient hydroxypropyl-β-cyclodextrin in the intravenous infusion therefore, the duration of use with the intravenous infusion should be kept to a minimum. Oral administration should be selected for participants for whom oral administration is possible. Also, the effect of renal impairment on letermovir PK was evaluated in participants with moderate (eGFR ≥30 to 59 mL/min/1.73 m^2) or severe renal impairment (eGFR <30 mL/min/1.73 m2; actual range: 11.86-28.14 mL/min/1.73 m^2) [Kropeit, D., et al 2017]. Based on the P006 study results, no dose adjustment is

recommended for participants with moderate or severe renal impairment. The approved letermovir dose for IV formulation is the same as PO dosing of 480 mg QD (or 240 mg QD with concomitant CsA). IV formulation should only be used when participants are either unable to swallow or have a condition that may interfere with the absorption of the oral formulation. Use of the IV formulation should generally be limited to 4 weeks or less in duration per participant.

4.3.2 Maximum Dose Exposure for This Study

The maximum dose of letermovir in this study will not exceed 480 mg once daily.

4.3.3 Rationale for Dose Interval and Study Design

Most HSCT patients are at highest risk for CMV disease within 14 weeks (~100 days) after transplantation. Antiviral prophylaxis with letermovir was efficacious when used for 84 days in the Phase 2b (MK-8228-020) study, and it had also been confirmed that it's efficacious when used for 100 days in the Phase 3 (P001) study, Therefore, study intervention with letermovir will be used for antiviral prophylaxis through Week 14 (~100 days) post-transplant in this study. Participants will then be followed through Week 24 post-transplant (additional 10 weeks following completion of study intervention) in order to evaluate the incidence of late-onset CMV infection/disease during the post-treatment period.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

Male/Female Chinese adult participant of an allogeneic HSCT will be eligible for inclusion in this trial.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Recipient CMV IgG seropositivity [R+] (have seropositivity for CMV) at screening or have documented seropositivity for CMV within 1 year before HSCT.
2. Be receiving a first allogeneic HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant).
3. Have undetectable CMV DNA (as confirmed by the central laboratory) from a plasma sample collected within 5 days prior to allocation.
4. Be within 28 days post-HSCT at the time of allocation.

Demographics

5. Is an individual of any sex/gender, from 18 years to any years of age inclusive, at the time of providing the informed consent.

Female Participants

6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP
  OR

- A WOCBP and:
  - Uses an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 28 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
  - Has a negative highly sensitive pregnancy test (serum as required by local regulations) within 24 hours before the first dose of study intervention.
  - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study.

Additional Categories

8. Be able to read, understand, and complete diaries.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Received a previous allogeneic HSCT (Note: Receipt of a previous autologous HSCT is acceptable).
2. Has a history of CMV end-organ disease within 6 months prior to allocation.
3. Has evidence of CMV viremia at any time from either signing the ICF or the HSCT procedure, whichever is earlier, until the time of allocation.

   (Note: Evidence of CMV viremia as reported by central lab will include reporting of CMV DNA test results as “detectable, not quantifiable” or “detected” with a numeric value provided.)
4. Has suspected or known hypersensitivity to active or inactive ingredients of letermovir formulations.

5. Has severe hepatic insufficiency (defined as Child-Pugh Class C [see Appendix 9]) within 5 days prior to allocation.
6. Has serum AST or ALT > 5 × the ULN or serum total bilirubin > 2.5 × ULN within 5 days prior to allocation.

   Note: Participants who meet this exclusion criterion may, at the discretion of the investigator, have **one** repeat testing done prior to allocation. 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. Is a) on renal replacement therapy (eg, hemodialysis, peritoneal dialysis) OR b) has end-stage renal impairment with a creatinine clearance ≤10 mL/min, as calculated by the Cockcroft-Gault equation using serum creatinine within 5 days prior to allocation.

   Creatinine Clearance (Males) = (weight in kg) (140 – age)(72) (creatinine in mg/dL)

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

   Note: Participants who meet this exclusion criterion may, at the discretion of the investigator, have **one** repeat testing done within 5 days prior to allocation. 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).
8. Has both moderate hepatic insufficiency AND moderate to severe renal insufficiency.

   Note: Moderate hepatic insufficiency is defined as Child-Pugh Class B (see Appendix 9); 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.
9. Has an uncontrolled infection (such as any infectious process that is associated with sepsis, septic shock and/or requires management in the intensive care unit) on the day of allocation.
10. Any rapidly-progressing disease or immediately life-threatening illness (including respiratory failure and septic shock) necessitating the use of IV fluids and/or vasopressors for maintaining blood pressure and/or the use of mechanical ventilation.
11. Has a documented positive result for human immunodeficiency virus antibody (HIV-Ab) test at any time prior to allocation, or for HCV-Ab with detectable HCV RNA, or hepatitis B surface antigen (HBsAg) within 90 days prior to allocation. Local HIV, HBV, or HCV lab testing using acceptable methods are allowed.
12. Has active solid tumor malignancies with the exception of localized basal cell or squamous cell skin cancer or the condition under treatment (e.g., lymphomas).
13. 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 intervention.

Prior/Concomitant Therapy

14. Received within 2 days prior to treatment initiation of letermovir or plans to receive during the study any of the following:
    - Ganciclovir
    - Valganciclovir
    - Foscarnet

- Acyclovir (at doses greater than those recommended for HSV/VZV prophylaxis >3200 mg PO per day or >25 mg/kg IV per day; see Section 6.5.2.1)
- Valacyclovir (at doses greater than those recommended for HSV/VZV prophylaxis, such as >3000 mg PO per day; see Section 6.5.2.1)
- Famciclovir (at doses greater than those recommended for HSV/VZV prophylaxis >1500 mg PO per day; see Section 6.5.2.1)

Received within 30 days prior to screening or plans to receive during the study any of the following:

- Cidofovir
- CMV hyper-immune globulin|
- Any investigational CMV antiviral agent/biologic therapy

15. Participant is anticipated to be treated with Traditional Chinese Medicine or herbal medicine during the study treatment period and for 14 days after study medication.

Prior/Concurrent Clinical Study Experience

16. Is currently participating or has participated in a study with an unapproved investigational compound or device within 28 days or 5× half-life of the investigational compound, whichever is longer, or 5× half-life of monoclonal antibody 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.
17. Has previously participated 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 this study.

Diagnostic Assessments

Not applicable.

Other Exclusions

18. 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 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.
19. 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

No lifestyle restrictions are required based on the study procedures.

5.3.1 Meals and Dietary Restrictions

The oral formulation of letermovir 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 letemovir must avoid consumption of grapefruit and grapefruit juice from 2 weeks prior to study treatment administration with CsA until 72 hours after the final administration of study treatment with CsA).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently allocated in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the 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 intervention 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 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 interventions to be used in this study is outlined in Table 1. In this study, approximately 120 participants will be allocated to receive letermovir once a day from the day of allocation (Day 1, within 28 days post-transplant) through 14 weeks (~100 days) post-transplant. Both oral (tablet) and IV formulations of letermovir will be used in this study.

Participants will be initiated with the oral formulation of study intervention provided they are able to swallow and do not have a condition (e.g., vomiting, diarrhea, or a malabsorptive condition) that may interfere with the absorption of the tablets. Participants requiring the oral 480 mg dose of letermovir should be initiated with two 240 mg tablets.

For participants who cannot tolerate swallowing and/or develop a condition that may interfere with the absorption of the oral formulation at or after allocation/Day 1, study intervention can be initiated/switched to the IV formulation. 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. Simultaneous use of IV and oral study intervention is **not** allowed. The IV formulation should be switched to oral study intervention (ie, at the next planned dose) as soon as such participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Letermovir	Experimental	Letermovir	Drug	Tablet	240 mg	240 mg (for participants on CsA) OR 480 mg (for participants not on CsA)	Oral	Through Week 14 (~100 days) post-transplant	Test Product	IMP	Sponsor
Letermovir	Experimental	Letermovir	Drug	Concentrate	240 mg	240 mg (for participants on CsA) OR 480 mg (for participants not on CsA)	IV Infusion	Through Week 14 (~100 days) post-transplant	Test Product	IMP	Sponsor

CsA = Cyclosporin A; IMP = Investigational Medicinal Product.

For letermovir oral route of administration, the study intervention will be dispensed every 2 weeks; one letermovir 240 mg tablet should be taken for the 240 mg dose, and two 240 mg letermovir tablets for the 480 mg dose.

For letermovir IV route of administration, letermovir 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. The dosing volume will be 250 mL and duration of infusion will be 60 minutes.Site personnel will administer the IV study medication through a sterile 0.2 micron or 0.22 micron PES in-line filter, using only IV bags and infusion set materials that are DEHP-free.

The letermovir IV formulation should be switched to oral study intervention (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.

Study intervention may begin as early as the day of transplant to no later than 28 days posttransplant, once the participant is determined to be negative for CMV viremia (no evidence of CMV viremia confirmed by the central laboratory on a sample collected from the participant within 5 days prior to allocation).

All supplies indicated in Table 1 will be provided per the “Sourcing” column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be assigned to a single intervention group.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment for ≥7 consecutive 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 Intervention

Letermovir is both a CYP3A inhibitor and substrate, an OATP1B1/3 inhibitor, and a CYP2C9 and CYP2C19 inducer. The following medications/therapies are allowed when coadministered with study intervention 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 product circular).

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

- **CYP3A substrates:**
  - Coadministration of letermovir with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of coadministered 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 letermovir (a moderate CYP3A inhibitor). Please consult current prescribing information for monitoring and dosing of these products with moderate inhibitors of CYP3A.
    - CsA: Coadministration of letermovir with CsA increases CsA concentrations. Frequent monitoring of CsA whole blood concentrations should be performed during and at discontinuation of letermovir with the dose of CsA to be adjusted as appropriate.
    - Sirolimus: Coadministration of letermovir with sirolimus increases concentrations of sirolimus. Frequent monitoring of sirolimus whole blood concentrations should be performed during and at discontinuation of letermovir with the dose of sirolimus to be adjusted as appropriate. When letermovir is coadministered with CsA, refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with CsA.
    - Tacrolimus: Coadministration of letermovir with tacrolimus increases tacrolimus concentrations. Frequent monitoring of tacrolimus whole blood concentrations should be performed during and at discontinuation of letermovir with the dose of tacrolimus to be adjusted as appropriate.

- Everolimus: Coadministration of letermovir with everolimus may increase everolimus concentrations. Frequent monitoring of everolimus blood concentrations should be performed during and at discontinuation of letermovir with the dose of everolimus to be adjusted as appropriate. (**Note:** Please see Section 6.5.2.2 for recommendation of everolimus when Letermovir is coadministered with CsA).
- Amiodarone: Letermovir 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 coadministered with letermovir.

- **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 letermovir is coadministered with CsA).
  - Fluvastatin, lovastatin, rosuvastatin, or pravastatin: The dose of fluvastatin, lovastatin, rosuvastatin, or pravastatin may need to be adjusted when coadministered with letermovir. Monitoring for statin-associated adverse reactions (eg, myalgias, rhabdomyolysis) is recommended during coadministration with letermovir.

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

  - Voriconazole: Coadministration of letermovir 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: Letermovir 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 coadministered with letermovir.
  - Proton Pump Inhibitors, omeprazole, and pantoprazole: Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.

- **Medications for Diabetes:**

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

6.5.2 Prohibited Medications

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

If there is a clinical indication for one of these or other medications specifically prohibited during the study, discontinuation from study intervention 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 intervention 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

Letermovir use that is not part of study medication is prohibited during treatment period and all of follow-up period.

The following medications/therapies are prohibited during treatment period and all of follow-up period (except for cases of suspected clinically significant CMV infection):

- Antiviral drugs or therapies for prevention/treatment of CMV, <u>including but not limited to</u>:
  - 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 PO per day)
  - Famciclovir (at doses greater than those recommended for HSV/VZV prophylaxis, such as >1500 mg PO per day)
  - CMV immunoglobulin
  - ANY investigational CMV antiviral agent/biologic therapy, including CMV vaccines

    <u>Note: these agents may be used for other indications while participants are on study intervention (eg, foscarnet for the treatment of HHV 6 or acyclovir for treatment of disseminated zoster)</u>

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.
- Traditional Chinese Medicines or Herbal Supplements: both Traditional Chinese medicines and Herbal Supplements are not permitted.
- CYP3A substrates with NTR, including but not limited to:
  - Pimozide: Concomitant administration of letermovir may result in increased concentrations of pimozide due to inhibition of CYP3A by letermovir, which may lead to QT prolongation and torsade de pointes.
  - Ergot alkaloids: Concomitant administration of letermovir may result in increased concentration of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, 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 letermovir is coadministered with CsA):
  - Simvastatin and pitavastatin
- 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 Coadministered with CsA

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on coadministered drugs may be different when letermovir is coadministered with CsA than when drugs are coadministered with letermovir 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 letermovir *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 Chinese product circulars for CsA, including the complete list of prohibited medications including those that are contraindicated or not recommended.

- Certain HMG-CoA reductase inhibitors (statins): When letermovir is coadministered with CsA, the magnitude of the increase in statin plasma concentrations is expected to be greater than with letermovir alone.
  - atorvastatin and lovastatin (**Note:** please see Section 6.5.2.1 for additional prohibited statins when coadministered with letermovir alone).

- Everolimus (**Note:** please see Section 6.5.1 for recommendation of everolimus when coadministered with letermovir alone)
- Repaglinide (**Note:** please see Section 6.5.1 for recommendation of repaglinide when coadministered with letermovir 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) during the study intervention period (ie, prior to completion or early discontinuation of study intervention), study intervention will be discontinued, and the participant may be treated according to the standard of care (SOC) (outside the context of the study). In this setting, any of the prohibited anti-CMV medications (as outlined in Section 6.5.2) may be used.

6.6 Dose Modification (Escalation/Titration/Other)

Please see Section 6.1 for letermovir dose to be used with or without coadministered CsA and Section 8.10.2.2 for information regarding dose modifications if CsA is initiated or discontinued during study intervention treatment period.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not Applicable. This is a single-arm study.

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 before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study Section 7.2.

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.

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 develops confirmed or suspected clinically significant CMV infection as determined by the investigator (see Section 4.2.1.1).
- The participant has a confirmed positive pregnancy test.
- The participant's investigator feels it is in the best interest of the participant to discontinue.
- An elevated AST or ALT lab value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
- The participant develops:
  - Both moderate hepatic insufficiency (Child-Pugh Class B; Appendix 9) and moderate-to-severe renal insufficiency (defined as CrCl <50 mL/min as calculated by the Cockcroft-Gault equation; see Section 5.2),

    OR
  - Severe hepatic insufficiency (Child Pugh Class C; Appendix 9),

    OR

  - Is a) on renal replacement therapy (eg, hemodialysis, peritoneal dialysis) OR b) has end-stage renal impairment with a creatinine clearance ≤10 mL/min, as calculated by the Cockcroft-Gault equation

- The participant may be discontinued from study intervention for any of the following reasons:
  - Any AE/SAE assessed by the investigator as possibly or probably related to study intervention. 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 intervention.
  - 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, places the participant at unnecessary risk through continued participation in the study or 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]).

Specific details regarding procedures to be performed at study intervention discontinuation are provided in 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.

Participants may be allowed to begin study medication again if deemed medically appropriate. 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 participant. 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 intervention to be restarted at the investigator's discretion, once PET is discontinued. In such instances, study intervention should be restarted <7 days from the date on which study intervention was stopped. **It is important to note that the status of the participant's study intervention in IRT should NOT be changed until the CMV DNA PCR result is confirmed and the investigator is certain that study intervention 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 intervention 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 8.1.10 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 (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- 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 used for screening or baseline purposes provided the procedures meet 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 is specified in a separate document.

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 informed consent from each potential participant (or their legally acceptable representative) prior to participating in this 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 documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the 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 or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

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 at screening and prior to allocation on Day 1.

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 documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care 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.

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. This includes review of consumption of grapefruit, Seville oranges or their respective juices, and other quinine-containing drinks or food. Prior medication taken by the participant within 30 days prior to the first dose of study intervention will be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant through 2 weeks after the study treatment period.

In addition, anti-CMV medications (including letermovir 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 24 posttransplant (Visit 21).

During the follow-up period through Week 24, concomitant medication review and recording of data is limited to anti-CMV medications and, all antimicrobials (antibacterials, antifungals, antiparasitic agents, and antivirals), oral hypoglycemic agents, insulin, granulocyte colony-stimulating factor (G-CSF), and immunosuppressant agents. Refer to the data entry guidelines for additional requirements on concomitant medication review and recording of data.

8.1.6 HSCT Details Review

All relevant data about the HSCT will be collected on Day 1. This includes details regarding conditioning regimen, date and type of transplant, source of stem cells, type of graft manipulation, presence of GVHD, and GVHD prophylaxis regimen (if any).

8.1.7 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 before intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.8 Assignment of Treatment/Randomization Number

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

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

8.1.9 Study Intervention Administration

The first dose of study intervention will be administered at the study site at Visit 2 (Day 1; within 28 days 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 letermovir IV formulation would be administered. The 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.

Participants should be switched from the IV formulation back to oral study intervention 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.

The study pharmacist will be responsible for the preparation of the IV study intervention. The IV study intervention will be administered by site personnel. Refer to the Pharmacy Manual for further details.

Study intervention may be interrupted for any reason for a time period of <7 consecutive days (including suspected CMV disease/infection; see Section 8.10.4). Study intervention interruption for a time period of <7 consecutive days due to an AE followed by re-starting of study intervention upon resolution of the AE is permitted.

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

8.1.9.1 Timing of Dose Administration

Study intervention 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 intervention 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.

8.1.9.2 Study Medication Diary and Recording the Study Intervention

For hospitalized participants receiving either letermovir oral tablets or IV formulation, study intervention will be recorded in the participant's chart; this will serve as the source document. For participants receiving oral tablets outside of the hospital setting (ie, receiving oral letermovir at home), study intervention will be recorded in a paper study medication diary (SMD). The investigator/study coordinator will review and provide instructions to the participant on the use of the SMD, which is to be completed during the treatment period of the study.

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.

If oral medication is administered by clinical personnel during any hospitalization, the site personnel will be responsible for transferring the appropriate information from the participant's medical record to the case report form.

When administering IV formulation of study medication, the volume and the duration of infusion will be documented. The investigator/study coordinator will be responsible for transferring the appropriate information to the case report form.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit 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).

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

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 are 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).

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 7 days after PET initiation (preferably within 48-72 hours). Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

8.2.2 CMV Serology (IgG) Testing

Available CMV serology (IgG) testing data for the participant will be obtained from the participant's chart. For participants whose CMV serology (IgG) testing data are not previously documented within 1 year before HSCT, CMV serology (IgG) testing should be performed locally per SOC at the site.

8.2.3 CMV Disease Assessment

CMV disease will be assessed at every visit from screening through Week 24 post-transplant. Diagnostic criteria for the evaluation of CMV infection are outlined in Appendix 8. If a participant develops suspected or confirmed CMV disease, 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 8 will be collected.

For participants who develop suspected or confirmed CMV disease: Clinical and laboratory evaluation of participants with suspected or confirmed CMV disease may be performed at the discretion of the site investigative team and at any time during the study intervention or follow-up period. During such evaluations, if a blood sample for CMV viral DNA testing is collected for processing by a local laboratory by the site investigative team, clinical decisions and management will be made based on the results of the local CMV DNA PCR results and assessment of the participant's CMV disease. When a CMV DNA PCR is collected for processing by a local laboratory, it is mandatory that a separate blood sample also be collected for CMV DNA PCR and sent to the central laboratory for processing.

Note: It is mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory **immediately prior to** (ie, on the day of) initiating treatment for confirmed or suspected CMV disease. In the event that the confirmatory result obtained on the day of anti-CMV treatment 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 7 days after PET initiation (preferably within 48-72 hours).

If the investigator decides to initiate PET or treatment for confirmed or suspected CMV disease while the participant is on study treatment, the participant's study intervention will be discontinued (see following bullet) and a CMV Infection Visit (including collection of CMV DNA PCR sample; see Section 1.3 [SoA]) will be completed prior to initiating treatment for CMV disease. These participants will complete all remaining treatment-period visits through Week 14 as well as all remaining visits through Week 24 as outlined in the SoA (Section 1.3). All specified procedures through Week 14 will be completed for these participants with the exception of study intervention administration and study medication diary review.

- Following the CMV Infection Visit, a participant may interrupt study treatment (if the participant is on study treatment at the time of the CMV Infection Visit) and receive treatment for CMV Disease for up to 7 days before the participant is permanently discontinued from study treatment (but remains in the study). If within the 7-day interval, CMV Disease is either not confirmed by the site investigator and/or an alternative medical condition that is not CMV-related is identified, then the participant may stop treatment for CMV disease and resume previously assigned study treatment.

If CMV disease is suspected or confirmed by the investigator during the post-treatment follow-up period (ie, after completion or early discontinuation of study intervention): Participants may be started on treatment for CMV disease at the investigator's discretion and will complete all remaining follow-up visits (through Week 24). See Section 1.3 SoA for procedures performed at the CMV Infection Visit.

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 prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in in a separate document.

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

8.3.1 Physical Examinations

At screening, on Day 1 (allocation), a complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

After Day 1, a targeted physical examination should be performed only if a participant has any complaints. Investigators should pay special attention to clinical signs related to previous serious illnesses. The content of the targeted physical examination will be at the discretion of the investigator. The timing of physical examinations is indicated in the Study SoA (Section 1.3).

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 10 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 resting 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 9. At the screening visit, the clinical assessment and the laboratory parameters

(total bilirubin, albumin, and 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 Birth Control Confirmation (WOCBP Only)

WOCBP must use acceptable methods of contraception from the time of consent through 28 days after the last dose of study intervention (see Appendix 5). Confirmation must be obtained by site personnel that participants and their partner(s) are using acceptable methods of contraception. This assessment must be documented in the participant's study chart at each specified visit.

No contraception measures are needed during letermovir treatment for male participants (refer to the Investigator's Brochure).

8.3.6 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 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, Serious Adverse Events, 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 need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, 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 participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; 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 intervention allocation through 14 days after cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

After 14 days following cessation of study intervention, only SAEs will be reported through Week 24 post-transplant.

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

Investigators are not obligated to actively seek AEs or SAEs 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 the investigator 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 2.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 2 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (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

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
ECI (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 (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse 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 AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, 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 allocated 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 toward 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. The

Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for 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 SAEs) 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), or a pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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

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

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory

value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
*Note: These criteria are based on 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

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Visit Requirements

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

8.10.1 Screening

Participants may be screened during a period starting from 15 days prior to transplant through 28 days post-transplant (laboratory test results necessary for allocation must be available within 5 days prior to the planned day of allocation). The informed consent must be obtained before any study-specific procedure is performed. It is acceptable that the date of obtaining informed consent is earlier than the day of performing screening procedures.

However, once informed consent is obtained adverse event reporting must be conducted according to Section 8.4.1.

Potential participants will be evaluated to determine if they fulfill the trial entry requirements as described in Section 5.1 and Section 5.2. The investigator will discuss with each potential participant the nature of the study and its requirements/restrictions. CMV serology (IgG) testing should be performed locally per SOC at the site; CMV seropositivity previously documented within 1 year before HSCT is acceptable. Donor CMV serostatus may either be positive (D+) or negative (D−). All screening procedures listed under Visit 1 of the SoA (Section 1.3) will be performed. Participants will be instructed that they are required to use methods of birth control as indicated in Appendix 5 during the protocol-defined time frame in Section 5.1.

For screening purposes, values from the participant's chart within 5 days prior to allocation for required chemistry, hematology, and urinalysis tests are acceptable. Documented negative HIV test results within 90 days prior to allocation of the participant will be acceptable. A copy of report must be available. If documentation of a previous HIV test is not available, the HIV test must be conducted using the local laboratory. Hepatitis B, and hepatitis C screening should only be performed if not previously documented within 90 days at any time prior to allocation. If hepatitis C virus antibody is positive, RNA PCR results should be provided (or, if not available, RNA PCR testing will be performed by the local laboratory).

CMV procedures/assessments will also be performed at screening. For initial screening, results of CMV DNA PCR assay performed at a local laboratory will be acceptable to establish absence of CMV viremia. Thereafter, CMV DNA PCR testing will be performed once a week by the central laboratory in order to exclude those with active CMV replication prior to study intervention initiation.

On the day of allocation, eligibility for enrollment into the study should be confirmed. At that time, participants have already received their HSCT and will be considered eligible for allocation once (a) they are determined to be negative for CMV viremia (**NO** evidence of CMV viremia from a central or local laboratory at any time point **and** confirmed by the central laboratory on a sample collected from the participant within 5 days prior to allocation), and (b) have acceptable creatinine clearance and liver function test values (i.e., within the range allowable in this study, as outlined in Section 5.2 [Exclusion Criteria]) from testing performed within 5 days prior to allocation. **(NOTE: Evidence of CMV viremia as reported by the central lab will include reporting of test results as "detectable, not quantifiable" or "detected" with a numeric value provided.)**

Presence of CMV disease in the screening period will be assessed according to Appendix 8.

8.10.2 Treatment Period

Study intervention (letermovir) may begin as early as the day of transplant and no later than 28 days post-transplant. Study intervention will continue through Week 14 (~100 days) post-transplant. For participants receiving the oral formulation of study intervention, letermovir tablets will be dispensed on Day 1 and every 2 weeks starting from Week 2. Visit schedules

must align the weekly visits with the drug dispensation every 2 weeks. Study intervention visits will occur weekly through Week 14 (~100 days) post-transplant.

The Day 1 Visit (as shown in the SoA, Section 1.3) will be day the participant is allocated and study intervention is initiated. Study intervention will continue through the End of Study Intervention Visit. The End of Study Intervention Visit may occur at the Week 10, 11, 12, 13, or 14 Visit depending on when study intervention is started during the 28-day post-transplant window. For example, if study intervention is started on the day of transplant, the End of Study intervention Visit will be the Week 14 Visit (which corresponds to Week 14 post-transplant). If study intervention is started 28 days post-transplant, the End of Study intervention Visit will be the Week 10 Visit (which corresponds to Week 14 post-transplant).

All procedures listed under the weekly study intervention 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 if a participant has any complaints. After allocation, vital signs should only be performed if targeted physical examination is performed.

8.10.2.1 Day 1 Visit

Day 1 procedures/assessments listed on the SoA must be performed prior to initiation of study intervention.

Laboratory safety evaluations (hematology, chemistry, and urinalysis) specified in Section 8.3.6 will be performed prior to study intervention initiation.

For female participants, a urine pregnancy test will be performed at the site prior to study intervention initiation. If the urine 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 pregnancy result is positive, the participant must not be allocated.

8.10.2.2 Study Intervention Administration

Following completion of the Day 1 procedures/assessments and confirmation of eligibility (including availability of results from samples for CMV DNA PCR, creatinine clearance, and liver function tests), the participant will be allocated. The site pharmacist or study coordinator will contact the IVRS for assignment of the study intervention to be administered. Sites should not call the IVRS for study intervention administration until the participant has met all criteria for the study and is ready to receive the first dose of study intervention on Day 1.

The first dose of study intervention will be administered at the Day 1 Visit. The oral or IV formulation of letermovir will be dispensed via the IVRS. Participants will be initiated with the oral (tablet) formulation of study intervention provided they are able to swallow and do not have a condition (e.g., vomiting, diarrhea, or a malabsorptive condition) that may interfere with the absorption of the tablets. For participants who cannot swallow and/or have a condition that may interfere with the absorption of the oral formulation, study intervention can be initiated with or switched to the IV formulation. The IV formulation should be

switched to oral study intervention (i.e., at the next planned dose) as soon as such participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves. Use of the IV formulation should generally be limited to 4 weeks or less in duration. 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.

The same dose of letermovir will be administered for both formulations. Participants will receive either 240 mg letermovir QD, if receiving concomitant CsA, or 480 mg letermovir QD, if not on CsA. If CsA is initiated after starting study intervention, the next dose of letermovir (administered up to 24 hours later) should be decreased to 240 mg QD. If CsA is discontinued permanently or for the long-term in a participant, the next dose of letermovir (administered up to 24 hours later) should be increased from 240 mg to 480 mg QD. If CsA is temporarily held due to high levels detected by therapeutic blood monitoring, the dose of letermovir need not be adjusted.

The 240 mg oral (tablet) formulation of letermovir will be available for study intervention (two 240 mg letermovir tablets should be taken for the 480 mg dose and one 240 mg tablet for the 240 mg dose). After Day 1, study intervention will continue through Week 14 (~100 days) post-transplant. During this period, samples for CMV DNA PCR should be sent a**t every visit** to the **central laboratory** as per the SoA (Section 1.3). The CMV DNA PCR test may be conducted within 3 days prior to a scheduled study visit and no later than the day of the scheduled study visit. (This CMV DNA PCR testing window is not applicable to a CMV Infection Visit. See Section 8.2.1.)

Participants will be trained in the use of the Study Medication Diary. Once the participant is discharged from the hospital, he/she will be instructed to enter the number of tablets of study intervention taken during the study intervention period.

8.10.3 Follow-up Period/Visits

After the last day of study intervention, participants will continue to be followed though Week 24 (~6 months) post-transplant. Visits will occur every 2 weeks from Week 15 post-transplant to Week 24 post-transplant, and all procedures listed in the SoA (Section 1.3) corresponding to the visits will be performed.

During the follow-up period, samples for CMV DNA PCR should be sent **at every visit** to the **central laboratory** as per the SoA (Section 1.3). The CMV DNA PCR test may be conducted ±4 days of the scheduled study visit. (This CMV DNA PCR testing window is not applicable to a CMV Infection Visit. See Section 8.2.1.)

Adverse event monitoring should include the collection of all adverse events while on study intervention and for 14 days following completion of study intervention (i.e., through Follow-up Week 2 Visit) in all participants, including those who have discontinued study intervention but are continuing in the study. Thereafter, only SAEs will be collected through Week 24 post-transplant in all participants, including those who have discontinued study intervention but are continuing in the study.

8.10.4 CMV Infection or Early Discontinuation Visit

The CMV Infection Visit will be performed for all participants who will be discontinued from study intervention due to clinically significant CMV infection requiring either treatment of disease or initiation of PET. It is very important to ensure that all procedures, as outlined in the SoA (Section 1.3), are performed at the CMV Infection Visit **immediately prior to** the initiation of treatment of CMV diseases or initiation of PET (i.e., on the day anti-CMV intervention is initiated). Most importantly, a confirmatory plasma sample for CMV PCR testing at the central laboratory should be collected at this visit.

After this visit, such participants will continue to be followed in the study and complete all remaining visits (including all subsequent treatment period visits) through Week 24 post-transplant as outlined in the SoA (Section 1.3). All specified procedures during the study intervention period will be completed for these participants with the exception of study intervention administration and study medication diary review.

The CMV Infection Visit will also be performed for all participants who require either treatment for disease or initiation of PET after study intervention completion, during the follow-up period (after Week 14 through Week 24 post-transplant). It is very important to ensure that all procedures, as outlined in the SoA (Section 1.3), are performed at the CMV Infection Visit **immediately prior to** the initiation of treatment of CMV diseases or initiation of PET (i.e., 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.

After this visit, such participants will continue to be followed in the study and complete all remaining visits through Week 24 post-transplant as outlined in the SoA (Section 1.3).

Note: It is mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory **immediately prior to** (i.e., on the day of) initiating treatment for CMV disease or PET in **ALL** instances. In the event that the confirmatory result obtained on the day of PET initiation is **NOT** available (e.g., 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 7 days after PET initiation (preferably within 48-72 hours). The participant will be considered to have met the primary efficacy endpoint if this confirmatory laboratory result is positive.

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

Note on reinitiation of study intervention: There may be instances where confirmatory central lab test results for CMV DNA PCR obtained on the day of PET initiation may be negative (CMV DNA undetectable) and the investigator may wish to discontinue PET. The decision to stop PET in the event of a negative (CMV not detectable) confirmatory central

laboratory result collected on the day of PET initiation resides with the investigator caring for the participant. Therefore, in the event the confirmatory CMV DNA sample at PET initiation is negative for CMV viremia, the Sponsor will allow for protocol-defined study intervention (i.e., letermovir) to be restarted at the investigator's discretion, once PET is discontinued. In such instances, study intervention should be restarted within 7 days from the date on which study intervention was stopped. It is important to note that the status of the participant's study intervention in IVRS should NOT be changed until the CMV DNA PCR result is confirmed and the investigator is certain that study intervention will be permanently discontinued.

The Early Discontinuation Visit will be performed for all participants who are prematurely discontinued up to Week 24 post-transplant from the *study, not study intervention*. It is very important to ensure that all procedures, as outlined in the SoA (Section 1.3), are performed in such participants at this visit prior to discontinuing the participant from the trial. Most importantly, a plasma sample for CMV PCR testing at the central laboratory should be collected at this visit.

8.10.5 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

8.10.5.1 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 clinically significant CMV infection **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 24 post-transplant during the treatment period (with the exception of study medication administration and Study Medication Diary review) 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 24 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.

8.10.6 Survival Status

Updated survival status may be requested at any time, both during study conduct or after study completion, or after a participant 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 will be documented in an sSAP and referenced in the 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 9.2-9.12.

Study Design Overview	A Phase 3, open-label, single-arm clinical study to evaluate the efficacy and safety of MK-8228 (letermovir) for the prevention of clinically significant cytomegalovirus (CMV) infection in Chinese adult, CMV-seropositive allogeneic hematopoietic stem cell transplant (HSCT) recipient.
Treatment Assignment	All participants will be assigned to a single intervention group.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)
Primary Endpoint	Clinically significant CMV infection through Week 24 (~6 months) post-transplant
Secondary Endpoints	**Efficacy:** • Clinically significant CMV infection through Week 14 (~100 days) post-transplant • CMV disease through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant • Initiation of PET for documented CMV viremia through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant • All-cause mortality through Week 14 (~100 days) post-transplant and Week 24 (~6 months) post-transplant **Safety:** Number of participants experiencing • Adverse Events (AEs) • AEs resulting in study medication discontinuation
Statistical Methods for Key Efficacy Analyses	The efficacy analysis will be based on the FAS population. The proportion of participants with clinically significant CMV infection through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant will be provided. The corresponding 95% confidence interval via the Clopper-Pearson method will also be provided. The primary approach for handling missing data will be the Non-Completer =Failure (NC=F) approach.
Statistical Methods for Key Safety Analyses	The safety analysis will be based on the APaT population. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs and ECG parameters. Descriptive statistics will be provided for these safety parameters.
Interim Analyses	No interim analysis is planned in this study.

Multiplicity	No multiplicity adjustment is planned in this study.
Sample Size and Power	This is an estimation study with no hypotheses to be tested. The planned sample size is approximately 120 participants. For the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant, the study will allow estimation of this proportion among participants receiving letermovir with a 95% confidence interval with a half-width of ~10 percentage points, assuming approximately 16% of participants will be excluded from FAS due to detectable CMV DNA on Day 1 (based on the global pivotal study P001), and the underlying clinically significant CMV infection rate is 37.5% in the letermovir group.

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 is being conducted as a single-arm, open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participants treatment assignments after each participant is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule for study intervention assignment. Allocation number will be assigned via an IRT.

9.3 Hypotheses/Estimation

There are no hypotheses to be tested in this study. Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

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

The primary efficacy endpoint will be the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant, defined as the occurrence of either one of the following outcomes:

- Onset of CMV end-organ disease
  OR
- Initiation of anti-CMV PET based on documented CMV viremia (as measured by the central laboratory) and the clinical condition of the participant.

CMV end-organ disease will be determined using the definitions in Appendix 8 and confirmed by an independent CAC. The adjudication of cases by the CAC (i.e., the final CAC assessment) will take precedence over the investigator's assessment. Only the CAC-

confirmed cases of CMV end-organ disease will be included in the CMV end-organ disease category. However, investigator-assessed CMV end-organ disease cases which 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 detectable 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® 6800 System in the central laboratory. If 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, detectable CMV viral DNA alone without initiation of anti-CMV therapy will not be considered as a case for clinically significant CMV infection.

The secondary efficacy endpoints are:

1. The proportion of participants with clinically significant CMV infection through Week 14 (~100 days) post-transplant.
2. Proportion of participants with CMV disease through Week 14 post-transplant and Week 24 post-transplant.
3. Proportion of participants with initiation of PET for documented CMV viremia through Week 14 post-transplant and Week 24 post-transplant.
4. Proportion of participants with all-cause mortality through Week 14 post-transplant and Week 24 post-transplant.

9.4.2 Safety Endpoints

An initial description of safety endpoints is provided in Section 4.2.1.2.

All AEs will be collected through 14 days after last dose of study medication. Thereafter, only serious adverse events (SAEs) will be collected through Week 24 post-transplant.

Safety endpoints will be analyzed using a 3-tiered approach (see Section 9.6.2).

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 allocated participants who:

- receive at least one dose of study treatment, and

- have no detectable CMV viral DNA (measured by the central laboratory) on Day 1 (when study intervention is initiated).

A supportive analysis using the PP Set will be performed for the primary and secondary efficacy endpoints. The PP population is a subset of the FAS population, and it excludes participants due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints. Potential violations that may result in the exclusion of a participant from the PP population include:

- failure to reasonably adhere to the dosing schedule for the study treatment
- failure to comply with specific inclusion/exclusion criteria
- use of a prohibited concomitant medication during the treatment period that may impact on the efficacy assessment

The final determination on important protocol deviations will be made prior to the final database lock and will be documented in a separate memo.

9.5.2 Safety Analysis Populations

Safety analysis will be conducted in the APaT population, which consists of all allocated participants who received at least one dose of study treatment.

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

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

For the efficacy analysis, the proportion of participants with clinically significant CMV infection through Week 14 (~100 days) post-transplant and through Week 24 (~6 months) post-transplant will be calculated. The 95% CI will be calculated based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934]. The same method will be used to analyze all binary endpoints.

The primary efficacy analysis will be performed on the FAS population. A supportive analysis including those participants who had detectable CMV viral DNA on Day 1 will be provided. The primary approach for handling missing data will be the NC=F approach (see below for details). Supportive analyses using PP population and different approaches for handling missing data will also be conducted (see Table 3).

An additional analysis for the primary endpoint will be performed to assess the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-

transplant using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted, and Kaplan-Meier estimate for the proportion at certain time point will be provided.

Table 3 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach [a]	Statistical Method	Analysis Population	Missing Data Approach [b]
Proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant	P	95% Confidence Interval (Clopper-Pearson)	FAS	NC=F
	S	95% Confidence Interval (Clopper-Pearson)	PP	NC=F
	S	95% Confidence Interval (Clopper-Pearson)	FAS	DAO
Proportion of participants with clinically significant CMV infection through Week 14 (~100 days) post-transplant	P	95% Confidence Interval (Clopper-Pearson)	FAS	NC=F
	S	95% Confidence Interval (Clopper-Pearson)	PP	NC=F
	S	95% Confidence Interval (Clopper-Pearson)	FAS	DAO

a. P=Primary approach; S=Supportive approach.
b. NC=F: Non-Completer=Failure. Non-completers refer to participants who prematurely discontinued from the study. DAO=Data-As-Observed.

Summary statistics and 95% confidence intervals will be provided for the following secondary endpoints:

- Proportion of participants with CMV disease through Week 14 post-transplant and Week 24 post-transplant.
- Proportion of participants with initiation of PET for documented CMV viremia through Week 14 post-transplant and Week 24 post-transplant
- Proportion of participants with all-cause mortality through Week 14 post-transplant and Week 24 post-transplant.

An additional analysis for above secondary endpoints will be performed for the proportion using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted, and Kaplan-Meier estimate for the proportion at certain time point will be provided.

Missing Data Handling

The primary approach for handling missing data will be the Non-Completer = Failure (NC=F) approach to be consistent with the pivotal study (P001). Non-completers refer to participants who prematurely discontinued from the study and had a missing efficacy

outcome at the time point of interest (e.g., Week 24 post-transplant). These participants will be considered as failure. A participant who discontinued study medication but remained in the study follow-up will be not considered as a non-completer.

A secondary approach for handling missing data is the DAO. With this approach, any participant with missing value for a particular endpoint will be excluded from the analysis.

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, vital signs, and ECG measurements.

The proportion of participants with AEs in the broad categories of any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued study medication due to an AE will be provided along with the corresponding 95% CIs. In addition, deaths will be summarized in the same manner. The 95% CIs for the safety parameters will be calculated using the Clopper-Pearson method [Clopper, C. J. 1934].

The primary safety analysis will summarize the safety data for participants through 14 days following cessation of the treatment period. Safety analyses will be performed on the APaT population. Below Table 4 provides the analysis strategy for safety parameters.

Table 4 Analysis Strategy for Safety Parameters

Safety Endpoint	95% CI	Descriptive Statistics
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
Deaths	X	X
Specific AEs, SOCs or PDLCs (incidence ≥3 participants)	X	X
Specific AEs, SOCs or PDLCs (incidence <3 participants)		X
Change from Baseline Results (Labs, ECGs, Vital Signs)		X

95% CIs will be calculated using the Clopper-Pearson method.
Abbreviations: AE = Adverse event; ECG = electrocardiogram; SOC = System Organ Class; PDLC = Pre-Defined Limit of Change; X = results will be provided.

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

Missing safety laboratory, ECGs, or vital signs will be handled using the Data-as-Observed approach, that is, any missing value will be excluded from the analysis. The only exception is when a Baseline/Day 1 result is missing; this is be replaced with the latest pre-treatment result, if available.

9.6.3 Summaries of Baseline Characteristics and Demographics

Baseline characteristics for all allocated and treated participants will be summarized using descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and allocated, and the primary reasons for screen failure and discontinuation will be provided. Demographic variables (e.g., age, gender, and high and low risk), indication for HSCT, prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analysis is planned for this study.

9.8 Multiplicity

There will be no multiplicity adjustments in the analysis of this study.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analysis

This is an estimation study with no hypotheses to be tested. This study will allocate approximately 120 participants to receive letermovir and will allow estimation of the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant among participants receiving letermovir with a 95% confidence interval with a half-width of ~10 percentage points. This is based on the follow assumptions: 1) an approximately 16% of participants will be excluded from FAS due to detectable CMV DNA on Day 1 (based on the global pivotal study P001), then the evaluable number of participants in the FAS population will consist of 100 participants in total; 2) the underlying clinically significant CMV infection rate is 37.5% in the letermovir group. The primary efficacy objective will be assessed based on the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant. The expected rate of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant is 17.5% based on P001 and assuming letermovir is expected to be similarly active in Chinese participants as in P001. Since the primary approach for handling missing data will be NC=F approach, 20% was added to the expected incidence of clinically significant CMV infection through Week 24 (~6 months) post-transplant based on P001. The calculation is based on exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934] with 100 participants in letermovir expected to be included in the analysis and is carried out using RStudio V1.1.453. Table 5 summarizes estimates of the half-width of the confidence interval for letermovir group under various assumptions. The upper bound of the 95% confidence interval is less than 60.6% which is the rate of clinically significant CMV infection through Week 24 post-transplant in the placebo group in P001.

Table 5 Two-Sided 95% Confidence Intervals for the Proportion of Participants with Clinically Significant CMV Infection through Week 24 (~6 Months) Post-Transplant (FAS Population)

	Number of Failures [a] (%)	Two-Sided 95% Confidence Interval [b]
N=100	32 (32.0)	(23.0, 42.1)
	36 (36.0)	(26.6, 46.2)
	40 (40.0)	(30.3, 50.3)
	44 (44.0)	(34.1, 54.3)
	48 (48.0)	(37.9, 58.2)
a Based on Non-Completer = Failure approach. b Based on the two-sided exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).		

9.9.2 Sample Size and Power for Safety Analysis

This study will allocate 120 participants to receive letermovir. As this will be an estimation study, the sample size used in this study is not based on statistical considerations.

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 70% chance of observing at least one of that particular AE among 120 participants. If no AE of that particular type is observed among the 120 participants, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <3.0% (one in every 33 participants).

Table 6 gives the estimate of and the upper bound of the two-sided 95% Clopper-Pearson exact confidence interval for the underlying percentage of participants with an AE given various hypothetical observed number of participants with the AE. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934].

Table 6 Estimate of Incidence of AEs and Upper Bound of 95% CI Based on Hypothetical Numbers of Participants with AEs

Sample Size	Hypothetical Number of Participants with an AE (Estimate of Incidence, %)	Upper Bound of 95% CI [a] for the Underlying Percentage of Participants with an AE (%)
N = 120	0 (0.0)	3.0
	1 (0.8)	4.6
	4 (3.3)	8.3
	10 (8.3)	14.8
a. 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 response across various subgroups, the proportion of participants with clinically significant CMV infection through Week 24 (~6 months) post-transplant and associated 95% CIs will be calculated within each category of the following classification variables:

- Gender (Male, Female)
- Age (≤65, >65)
- High and low risk
- Haploidentical donor (Yes, No)
- CsA use (Yes, No)

The consistency of the response 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.

9.11 Compliance (Medication Adherence)

Drug accountability data for letermovir will be collected during the study. A day within the study will be considered an "On-Therapy" day if the participant takes at least one 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 treatment allocation to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from treatment allocation to the date of the last dose of study intervention.

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

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

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

In addition, percent of participants on CsA and duration of CsA use will be reported.

9.12 Extent of Exposure

The Extent of Exposure to study intervention will be evaluated by summary statistics (N, mean, and range) for the "Number of Days on Therapy".

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, 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 and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, 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 (e.g., 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 (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. 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 (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and 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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified 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. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

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. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), 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.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record review and medical evaluation 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 (e.g., 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, frequently 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

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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 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 before 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 Clinical Adjudication Committee (CAC)

A 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.

1. CMV disease, as defined in Appendix 8: This role is important to standardize the evaluation (ie, adjudication) of all suspected cases of CMV disease occurring during the trial.

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 ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the 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 trials 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 Debarment

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, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), 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 Trials.

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.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

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 participants' documented informed consent, 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. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution 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 or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the local lab except that CMV DNA PCR testing will be performed by the central lab.
- 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 7 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters			
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
	Nonfasting Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis	1. Specific gravity 2. Glucose, protein, blood 3. Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	1. Coagulation: INR[a] 2. Serum β human chorionic gonadotropin (β-hCG) pregnancy test (for WOCBP) 3. Urine β-hCG pregnancy test (for WOCBP)[b] 4. Serology: HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody[c] 5. HCV RNA PCR: to be done only in participants who test positive for HCV antibody 6. CMV Serology (IgG) Testing 7. CMV DNA PCR			

Laboratory Assessments	Parameters
NOTES: a. For screening, values from the participant's chart for required chemistry, hematology, coagulation, and urinalysis tests are acceptable. The following tests are to be performed within 5 days prior to allocation and results must be available prior to allocation: coagulation (INR), serum AST, ALT, and total bilirubin; creatinine clearance. If not available, this testing may be performed locally per SOC. b. Performed locally; serum pregnancy test must be performed to confirm a positive urine test result. c. Documented negative HIV results within 90 days prior to allocation is acceptable. HBV/HCV to be done if not documented within the previous 90 days. If hepatitis C virus antibody is positive, RNA PCR results should be provided.	

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 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 includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), 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 preexisting 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 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 preexisting condition that has not worsened is not an SAE.) A preexisting 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.

10.3.4 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.

10.3.5 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/toxicity

- 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 study intervention cause the AE?
- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? 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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention 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; (2) the study is a single-dose drug study; or (3) study intervention (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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION 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 study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their 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 study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- 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 their 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.

10.3.6 Reporting of AEs, SAEs, 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 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 email 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 and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not Applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal 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 Contraceptive Requirements

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 8 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 8 Contraceptive Methods

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] Failure rate of <1% per year when used consistently and correctly.
• Progestogen- only contraceptive implantc,[d] • IUSc,[e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This 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. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen- containing) hormonal contraceptionc,[d] o Oral o Intravaginal o Transdermal o Injectable
• Progestogen-only hormonal contraceptionc,[d] o Oral o Injectable
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 intervention. 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.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods).
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

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: Collection and Management of Specimens for Future Biomedical Research

Not Applicable.

10.7 Appendix 7: Country-specific Requirements

Not Applicable.

10.8 Appendix 8: 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

[Ljungman, P., et al 2016]

10.9 Appendix 9: Child-Pugh Classification for Severity of Liver Disease

	Scoring by Anomaly		
Signs or symptom	**1 point**	**2 points**	**3 points**
Hepatic encephalopathy[a]	absent	Grade 1 or Grade 2	Grade 3 or Grade 4
Ascites	absent	mild	moderate
Bilirubin	<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
INR[b]	<1.7	1.7 – 2.3	>2.3

a 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

b For participants with no known medical history of hepatic impairment or signs or symptoms attributable to hepatic impairment and on anticoagulation therapy within 10 days (inclusive) preceding the INR measurement, the corresponding INR value should be scored as 1 point for calculating the Child Pugh score for inclusion/exclusion and study discontinuation criteria.

INR = international normalized ratio

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

c 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.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
CAC	Clinical Adjudication Committee
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CL	clearance
CMV	cytomegalovirus
CrCl	creatinine clearance
CRF	Case Report Form
CsA	cyclosporin A
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CYP	Cytochrome P450
D+	CMV-seropositive donor
DAO	Data-As-Observed
DEHP	diethylhexyl phthalate
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate

Abbreviation	Expanded Term
EMA	European Medicines Agency
EU	European Union
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FSH	follicle stimulating hormone
FSR	First site ready
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GCV	ganciclovir
GI	gastrointestinal
GVHD	graft-versus-host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV-Ab	hepatitis C virus antibody
HIV	human immunodeficiency virus
HIV-Ab	human immunodeficiency virus antibody
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board

Abbreviation	Expanded Term
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
LLoQ	lower limit of quantification
MCV	mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
NC=F	Non-Completer=Failure
NIMP	Non-Investigational Medicinal Product
NTR	narrow therapeutic range
OF	observed failure
PCR	polymerase chain reaction
PES	polyethersulfone
PET	pre-emptive therapy
PK	pharmacokinetic
PO	orally
QD	once daily
RBC	red blood cell
RNA	ribonucleic acid
R+	CMV-seropositive recipient
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMD	Study medication diary
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

Abbreviation	Expanded Term
US	United States
VGCV	valganciclovir
VZV	Varicella zoster virus
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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