Official Protocol Title:	A Phase 3, Open-Label, Single-Arm Clinical Study to Evaluate the Safety, Efficacy and Pharmacokinetics of MK-8228 (Letermovir) for the Prevention of Human Cytomegalovirus (CMV) Infection and Disease in Adult Japanese Kidney Transplant
NCT number:	NCT04129398
Document Date:	01-Feb-2022

Title Page

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Protocol Title: A Phase 3, Open-Label, Single-Arm Clinical Study to Evaluate the Safety, Efficacy and Pharmacokinetics of MK-8228 (Letermovir) for the Prevention of Human Cytomegalovirus (CMV) Infection and Disease in Adult Japanese Kidney Transplant Recipients

Protocol Number: 042-03

Compound Number: MK-8228

Sponsor Name:

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

Legal Registered Address:

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Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	Not Applicable
EudraCT	Not Applicable

Approval Date: 01 February 2022

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 03	01-FEB-2022	The primary purpose of this protocol amendment is to clarify that the first database lock will be executed when all results of letermovir plasma concentrations become available.
Amendment 02	26-MAY-2020	The primary purpose of this protocol amendment is to add everolimus as a prohibited medication (when LET is co-administered with CsA) and as a medication to be administered with caution when co-administered with LET in Sections 6.5.1 and 6.5.2, respectively.
Amendment 01	11-DEC-2019	The primary purpose of this protocol amendment is to revise the description of sterile in-line filters to be used during administration of intravenous formulation of LET to align with current Japan Prescribing Information for letermovir.
Original Protocol (Version 00)	24-JUN-2019	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [03]

Overall Rationale for the Amendments:

The primary purpose of this protocol amendment is to clarify that the first database lock will be executed when all results of letermovir plasma concentrations become available.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) Study therapy Administration/Dispensing	(X) added to Study therapy Administration/Dispensing on Week 1.	To align with the actual procedure.
2.1 Study Rationale	Underlined text deleted; Currently, there are … and 2) CMV pre-emptive therapy (PET), ie, active surveillance for CMV infection, typically by CMV deoxyribonucleic acid (DNA) level monitoring <u>(which is available but not reimbursed in Japan)</u> or the CMV pp65 antigen testing (which is widely available as standard of care [SOC] in Japan) and initiation of anti-CMV treatment upon detection of CMV viremia.	The test has now been approved and reimbursed in Japan.

Section # and Name	Description of Change	Brief Rationale
9.2 Responsibility for Analyses/In-house Blinding	Underlined text added; This trial is being conducted as an open-label study, ie, subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. <u>First database lock will be executed when all results of letermovir plasma concentrations become available for population PK and exposure-safety analyses to submit data to regulatory agencies. The results of the population PK and exposure-safety analyses will be reported in a Modeling and Simulation report. Final database lock will be executed at the end of the study for safety and efficacy analyses. Additional database lock(s) may be conducted if needed.</u>	To clarify that the first database lock will be executed when all results of letermovir plasma concentrations are available. By doing so, the availability of the PK data for analysis would be accelerated by approximately 6 months. These data will be included in the Population PK and exposure-safety analyses.
1.1 Synopsis Estimated Duration of Study and Duration of Participation 1.3 Schedule of Activities (SoA) Footnote d 4.4 Beginning and End of Study Definition 5.1 Inclusion Criteria (inclusion criterion #6) 8.1.1 Informed Consent 8.1.1.1 General Informed Consent	Updated wording of informed consent procedures/interactions. • written **original**: "written/signed informed consent" **revised**: "documented informed consent" • legal representative **original**: "participant/legal representative" **revised**: "participant or their legally acceptable representative" • contact **original**: Revised text from "study-related telephone-call or visit" **revised**: "study-related contact"	To align with updated informed consent text, as described in the Sponsor's core protocol template.

Section # and Name	Description of Change	Brief Rationale
8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 8.1.3 Participant Identification Card 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.8 Future Biomedical Research Sample Collection 8.9 Planned Genetic Analysis Sample Collection 10.1.8 Data Quality Assurance		
Throughout	Minor editorial and grammatical revisions.	To improve accuracy and clarity, and to ensure consistency of language across the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Open-Label, Single-Arm Clinical Study to Evaluate the Safety, Efficacy and Pharmacokinetics of MK-8228 (Letermovir) for the Prevention of Human Cytomegalovirus (CMV) Infection and Disease in Adult Japanese Kidney Transplant Recipients

Short Title: P3 Trial of MK-8228 (Letermovir) in Adult Japanese Kidney Transplant Recipients

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There are no hypotheses to be tested in this study.

In adult Japanese kidney transplant recipients who are organ donor (D) or organ recipient (R) seropositive (D+/R−, D+/R+ or D−/R+) for CMV:

Primary Objectives	Primary Endpoints
- To evaluate the safety and tolerability of letermovir based on the proportion of participants with adverse events.	- Adverse events (AEs) - Study drug discontinuations due to AEs
Secondary Objectives	Secondary Endpoints
- To evaluate the efficacy of letermovir in prevention of CMV disease and infection, as measured by the proportion of participants with adjudicated CMV disease or participants who have undergone anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) through Week 28 and Week 52 post-transplant.	- Adjudicated CMV disease OR anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local)
- To evaluate the efficacy of letermovir in prevention of CMV disease, as measured by the proportion of participants with adjudicated CMV disease through Week 28 and Week 52 post-transplant.	- Adjudicated CMV disease

- To evaluate the efficacy of letermovir in prevention of CMV infection, as measured by the proportion of participants with quantifiable CMV DNAemia (central) through Week 28 and Week 52 post-transplant.	- Quantifiable CMV DNAemia (central)
- To evaluate the pharmacokinetics of letermovir in Japanese kidney transplant recipients.	- Pharmacokinetic endpoints (the plasma concentrations of LET, PK parameters, ie, Oral: AUCtau, Ctrough, Cmax, Tmax, CLss/F; IV: AUCtau, Ctrough, Ceoi, CLss)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Prevention of CMV disease in adult kidney transplant recipients
Population	adult Japanese D+/R−, D+/R+ or D−/R+ kidney transplant recipients
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	None
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 30 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related study-related contact.

Number of Participants:

Approximately 20 participants (with at least 10 being D+/R−) will be allocated/enrolled.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Use</th></tr>
<tr><td>LET (for participants not on CsA)</td><td>480 mg</td><td>Once daily</td><td>Oral[a] or IV[b, c]</td><td>Experimental</td></tr>
<tr><td>LET (for participants on CsA)</td><td>240 mg</td><td>Once daily</td><td>Oral[a] or IV[b, c]</td><td>Experimental</td></tr>
<tr><td colspan="5"><u>Duration</u>: Interventions will be started within 7 days post-transplant and continue through Week 28</td></tr>
<tr><td colspan="5">LET = letermovir; CsA = cyclosporin A; IV = intravenous
a: Two 240 mg LET tablets should be taken for the 480 mg dose and one tablet for the 240 mg dose.
b: LET IV formulation dosing volume is 250 mL and duration of infusion will be 60 minutes. LET IV will be provided as a sterile liquid concentrate for dilution (20 mg/mL), two vials to be used for the 480 mg dose and one vial for the 240 mg dose.
c: The LET IV formulation should be switched to oral study therapy (ie, at the next planned dose) as soon as participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>1 (single-arm study)</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 52 weeks (for participants who receive a kidney from a deceased donor) or 54 weeks (for participants who receive a kidney from a living donor) from the time the participant provides documented informed consent through the final contact. After a screening phase of approximately 8 days for participants who receive a kidney from a deceased donor or up to 21 days for participants who receive a kidney from a living donor, each participant will be started on LET within 7 days post-transplant and receive LET through approximately Week 28. After the end of treatment each participant will be followed through approximately Week 52.</td></tr>
</table>

Study Governance Committees:

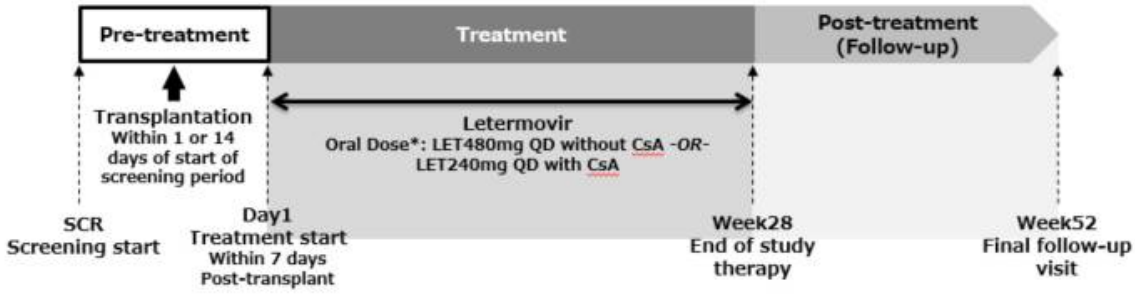
Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.



SCR = Screening; LET = Letermovir; QD = once daily; CsA = cyclosporin A

Screening of potentially eligible participants may begin as early as one day before transplantation for participants receiving a kidney from a deceased donor and 14 days prior to transplantation for participants receiving a kidney from a living donor. Screening should be completed by and including the day prior to Day 1.

* For participants who cannot tolerate swallowing and/or develop a condition that may interfere with the absorption of the oral formulation of LET at or after Day 1, study therapy can be initiated/switched to the IV formulation of LET.

Figure 1 Study Design

1.3 Schedule of Activities (SoA)

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for Future Biomedical Research	X																					
Inclusion/Exclusion Criteria	X		X																			Recheck clinical status before 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	
Intervention allocation			X																			

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
Kidney Transplant/ Dialysis Details Review			X																			
Study therapy Administration/ Dispensing			X	(X)	X	X	X	X	X	X	X	X	X									Start of study treatment is Day 1 (day of allocation). See Section 8.12.2.
Study Medication Reconciliation and Diary Review			X	X	X	X	X	X	X	X	X	X	X	X							X	
Safety Procedures																						
Full physical examination	X		X											X								
Height	X																					
Weight	X													X							X	
Directed physical examination				X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	Performed only when clinically indicated
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.3.2.

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
12-lead ECG	X				X									X							(X*)	Read locally. Screening values collected within 3 months prior to screening may be used. See Section 8.3.3. *Performed only if the Visit will occur at W28.
Child-Pugh Score	X		X	X	X	X	X	X	X	X	X	X	X	X								See Section 8.3.5 and Appendix 9.
Participant Confirmation of Birth Control (WOCBP only)	X		X	X	X	X	X	X	X	X	X	X	X	X	X						X	
AE/SAE Review	X		←																	→	X	Including infusion site reactions. See Section 8.3.7 and 8.4.

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
Hematology	X		X	X		X		X		X	X	X	X	X	X						X	Screening values from the participant's chart within 14 days prior to screening for required chemistry, hematology, coagulation, and urinalysis tests are acceptable. Screening test may be performed locally or centrally. Urinary tests can be waived if unable to provide urine. See Section 8.12.1.
Chemistry	X		X	X		X		X		X	X	X	X	X	X						X	
Coagulation: PT/INR	X		X	X	X	X	X	X	X	X	X	X	X	X	X						X	
Urinalysis	X		X											X	X						X	

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
Pregnancy Test (WOCBP only)	X																					Per pre-transplant SOC at the site (either urine or serum is acceptable).
Urine Pregnancy Test (WOCBP only)			X			X		X		X	X	X	X	X	X						X	Performed locally. May use central or local serum pregnancy test if unable to provide urine. See Section 8.12.2 and Appendix 2.
HIV and Hepatitis B and C Screen	X																					Screening values collected prior to screening (within 90 days for Hepatitis B and C) may be used. See Section 8.12.1.

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on “Day of Tp”.
CMV Procedures/Assessments																						
CMV Disease Assessment	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. See Section 8.2.1.1.
CMV DNA PCR			X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.1.2.
CMV Serology (IgG)	X																					Performed locally per SOC at the site if not previously documented (within 90 days prior to Day 1 in case of D+/R−).
QuantiFERON-CMV Assay	X									X				X			X			X	X	See Sections 4.2.1.2.1 and 8.2.4.

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
CMV Viral Resistance Testing[c]																				X	X	To be performed only for participants in whom study treatment is stopped (if on study treatment) and CMV treatment is started due to CMV disease or infection. See Section 8.2.2.
Health Outcomes Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.11.
Pharmacokinetics/Pharmacodynamics/Biomarkers																						
Blood for Genetic Analysis[d]	X																					

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
Trough PK and Week 1 Intensive PK			X	X*	X	X	X	X	X	X	X	X	X	X							X	Trough PK samples: Collected pre-dose in all participants at each visit of the treatment period and at CMV Infection/Early Discon visit (if during treatment period). *Week 1 Intensive PK: To be collected on Study Day 6, 7, 8, 9, or 10. See Sections 4.2.1.3 and 8.6.

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on "Day of Tp".
Additional Intensive PK for participants with dose formulation switch				◄										►								Performed at any time between 6th or more consecutive days until the 10th day after dose formulation switch. See Sections 4.2.1.3 and 8.6.

Study Period	Pre-treatment		Treatment												Follow-up						CMV Infection and/or Early Discon Visit	Notes
Visit Number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Visit Name	SCR[a]	Day of Tp	D1[b]	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52		Study visits are calculated relative to Day 1. If treatment discontinued early, all remaining visits should be completed.
Visit Window	-14d	-7d		±3d											±7d							Screening window is based on “Day of Tp”.

AE = adverse event; CMV = cytomegalovirus; D = Day, DNA = deoxyribonucleic acid; ECG = electrocardiogram; HIV = human immunodeficiency virus; IEC = independent ethics committee; IgG = immunoglobulin G; INR = international normalized ratio; IRB = institutional review board; OATP = organic anion-transporting polypeptide; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; SAE = serious adverse event; SCR = screening; SOC = standard of care; Tp = transplant; W = Week; WOCBP = women of childbearing potential

a. Screening should begin after obtaining documented consent and may begin on as early as one day before transplantation for participants receiving a kidney from a deceased donor and up to 14 days prior to transplantation for participants receiving a kidney from a living donor. All screening procedures listed under Visit 1 of the Study SoA will be performed and must be completed by one day prior to Day 1. See Section 8.12.1 regarding details of screening procedures.

b. Start of study treatment is Day 1 (day of allocation). Study therapy must begin within 7 days post-transplant and will continue through Week 28. Day 1 procedures/assessments must be performed prior to first dose of study treatment.

c. Once the CMV Infection Visit occurs, another plasma sample for CMV viral resistance testing should be collected at the next scheduled visit. Among these participants, a final sample for CMV viral resistance testing will also be collected at Week 52.

d. This sample will be drawn for SLCO1B1 (OATP1B1) and UGT1A1 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to SLCO1B1 (OATP1B1) and UGT1A1 genes. Leftover extracted DNA will be stored for FBR if the participant (or legally acceptable representative) provides documented informed consent for FBR.

2 INTRODUCTION

2.1 Study Rationale

Cytomegalovirus (CMV) is an opportunistic pathogen which causes infection (ie, virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen; Section 4.2.1.2) and disease (ie, end-organ involvement or CMV syndrome; Section 4.2.1.2 and Appendix 8) with substantial morbidity and mortality among solid organ transplant (SOT) recipients [Ljungman, P., et al 2016]. In a study describing the natural course of CMV disease over a 5-year period in kidney transplant recipients, the incidence of CMV infection among 477 kidney recipients was 63% over the first 100 days following transplantation [Husain, S., et al 2009] [Hartmann, A., et al 2006]. The incidence of CMV disease was the highest among CMV seronegative kidney recipients (R) with a transplanted kidney from CMV seropositive donor (D), ie, D+/R– patients (56%), followed by D–/R+ and D+/R+ patient groups (20%) [Husain, S., et al 2009] [Hartmann, A., et al 2006].

The clinical effects of CMV can be divided into direct and indirect effects [Boeckh, M. 2011]. Direct effects attributed to CMV include CMV syndrome or CMV end-organ disease [Humar, A., et al 2010] [Rubin, R. H. 2007]. Indirect effects of CMV may include an increased risk of allograft rejection [Humar, A., et al 2010] [Kranz, B., et al 2008], opportunistic infections (OIs), and post-transplant diabetes mellitus [Humar, A., et al 2010] [Hjelmesaeth, J., et al 2005]. CMV infection and disease, as well as the CMV-associated direct and indirect clinical effects present a substantial challenge to the clinical management of SOT recipients.

Currently, there are two clinical strategies for preventing CMV disease in the SOT recipient population: 1) CMV prophylaxis, ie, the post-transplant administration of anti-CMV medication such as valganciclovir (VGCV) for an extended duration (typically 200 days for D+/R− kidney transplant recipients; see below); and 2) CMV pre-emptive therapy (PET), ie, active surveillance for CMV infection, typically by CMV deoxyribonucleic acid (DNA) level monitoring or the CMV pp65 antigen testing (which is widely available as standard of care [SOC] in Japan) and initiation of anti-CMV treatment upon detection of CMV viremia. CMV prophylaxis is now widely used following SOT in the United States (US) and the European Union (EU) and has been associated with reductions in CMV disease, mortality, and graft rejection.

In Japan, an addendum for the 2011 guideline for CMV management in the kidney transplant patient population was issued in 2015 [Japanese Society for Clinical Renal Transplantation Guideline Work Group 2011; Addendum in 2015]. CMV prophylaxis with extended duration (200 days) of VGCV was recommended for high risk recipients (D+/R− patients who are treated for acute transplant rejection, received grafts from blood type incompatible donors or anti-donor antibody negative). The guideline also stated CMV prophylaxis with 200 days of VGCV 450 ~ 900 mg/day decreases the incidence of CMV disease as well as acute graft rejection and is the current SOC regimen for CMV prophylaxis in SOT recipients outside Japan. In 2016, VGCV was approved for the prevention of CMV disease in the SOT recipient population in Japan. However, VGCV is associated with myelotoxicity, which can

be clinically relevant for SOT recipients on concomitant immunosuppressive agents (eg, mycophenolate mofetil) and antibacterial prophylaxis (eg, trimethoprim/ sulfamethoxazole) that can also cause myelosuppression [Kidney Disease: Improving Global Outcomes Transplant Work Group 2009] [Razonable, R. R. 2013] [Martin, S. I., et al 2013]. Moreover, VGCV requires dose adjustments based on renal function [Japan Prescribing Information, VALIXA 2018] and CMV strains resistant to VGCV have been identified [Razonable, R. R. 2013] (Section 2.2.1). An effective and well tolerated prophylactic anti-CMV medication for SOT recipients that does not cause myelosuppression, is dosed independent of renal function, and is active against both wild type and VGCV-resistant CMV strains, remains an unmet medical need.

MK-8228 (also known as letermovir; hereafter referred to as LET) belongs to a new class of anti-CMV agents with a novel mechanism of action with:

(1) Significant anti-CMV activity in in vitro and in vivo pre-clinical studies [Japan Prescribing Information, PREVYMIS 2018];

(2) A favorable clinical safety profile demonstrated in Phase 1 and 2 studies, as well as in the Phase 3 P001 study in hematopoietic stem cell transplant (HSCT) recipients [Japan Prescribing Information, PREVYMIS 2018];

(3) Clinical efficacy as demonstrated in the P001 study in HSCT recipients [Marty, F. M., et al 2017]; and

(4) Activity against viral isolates resistant to marketed anti-CMV agents, also demonstrated in a case of multi-organ disease due to multi-resistant CMV [Kaul, D. R., et al 2011]. The activity of these agents map to the UL54 or UL97 genes, while LET activity maps to the UL56 (terminase) gene [Goldner, T., et al 2011].

Protocol 042 is planned to evaluate the safety, efficacy and pharmacokinetics (PK) of LET administered as prevention of CMV infection and disease in adult Japanese kidney transplant recipients. In addition to D+/R– kidney transplant recipients who are at the highest risk of CMV disease, R+ (either D+/R+ or D–/R+) patients will also be enrolled as such group of patients are also expected to benefit from prophylaxis. Duration of prophylaxis in R+ (either D+/R+ or D–/R+) kidney transplant recipients is noted in the overseas guideline [Kotton C.N., et al 2018]; while the general recommendation of prophylaxis for this group of patients is 3 months, an extended duration (between 3 and 6 months) of prophylaxis for the patients whose risk for CMV may be increased (eg, those on recent antilymphocyte therapy, desensitization) is suggested to be effective. Therefore, in this study, R+ patients may be enrolled if the investigator considers the patient would benefit from 200 days of prophylaxis, and all patients will be given 200 days of prophylaxis. Study treatment will be initiated within 7 days post-transplant and continue through Week 28. After approximately 28 weeks of study therapy, participants will be followed through Week 52 post-transplant (ie, approximately 12 months) to assess for late onset CMV infection and disease. The study visits are calculated relative to Day 1 and the reported data will be assessed relative to the day of transplant for efficacy analysis.

Details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying Investigator's Brochure (IB) and Informed Consent documents.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

VGCV has been approved for the prevention of CMV disease in SOT recipients at high risk in and outside of Japan. The results of the IMPACT study demonstrated that VGCV prophylaxis of 28 weeks (ie, 200 days) is more effective than 14 weeks (ie, 100 days) in reducing the incidence of CMV disease in non-Japanese D+/R− kidney transplant recipients [Humar, A., et al 2010].

However, VGCV is also associated with myelotoxicity as described in the VGCV label [Japan Prescribing Information, VALIXA 2018]. Moreover, antiviral drug resistance [Razonable, R. R. 2013], most commonly to VGCV and ganciclovir (GCV, approved only for treatment use in Japan), among CMV clinical isolates has emerged following widespread use of these drugs for CMV prophylaxis and PET. Drug resistance is usually seen after treatment duration with antiviral agents of weeks to months [Beam, E., et al 2012]. The majority of resistance mutations to VGCV and GCV are associated with mutations in the UL97 encoded viral protein kinase [Lurain, N. S. and Chou, S. 2010]. Resistance to VGCV and GCV also occurs via mutations in the viral DNA polymerase gene (UL54), often in the presence of UL97 mutations [Boivin, G., et al 2012].

LET is a novel inhibitor of the CMV terminase (UL56/UL89), an enzyme that plays an important role in the cleavage of newly synthesized concatenated CMV DNA into individual unit-length viral genomes that are subsequently inserted into CMV procapsids to generate infectious CMV virions [Goldner, T., et al 2011]. LET has demonstrated potent, selective, and reversible inhibition of CMV activity in preclinical studies in vitro and efficacy against the virus in vivo [Lischka, P., et al 2010] [Goldner, T., et al 2011]. As there is no human homologue for the DNA terminase, there is a limited potential for mechanism-based toxicity.

LET has been shown to be generally well tolerated in 31 Phase 1 studies, 2 Phase 2 studies, and a pivotal Phase 3 study, P001, in HSCT recipients. In P001, in which CMV seropositive allogeneic HSCT recipients including Japanese participants received LET or placebo from the early post-transplant period (within 4 weeks post-transplant) through Week 14 post-transplant and were followed for an additional 34 weeks, LET was superior to placebo in the prevention of clinically significant CMV infection (defined as onset of CMV end-organ disease OR initiation of anti-CMV PET based on documented CMV DNAemia as measured by the central laboratory and the clinical condition of the participant) through Week 24 post-transplant [Marty, F. M., et al 2017]. LET prophylaxis also resulted in lower all-cause mortality relative to placebo through Week 24 post-transplant and Week 48 post-transplant in HSCT recipients.

Based on its mechanism of action that is distinct from other available anti-CMV agents, patients who are given LET for prophylaxis and experience CMV infection or disease, ie, a clinical and/or virological CMV "breakthrough" event, are still expected to retain available treatment options using existing anti-CMV medications. This study will evaluate the safety, efficacy and pharmacokinetic of LET in the prevention of CMV infection and disease in adult Japanese D+/R− kidney transplant recipients.

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

Currently, there is one ongoing clinical study involving LET for adult SOT patients (P002; a Phase 3 randomized, multi-site, double-blind active comparator trial to evaluate the efficacy and safety of LET versus VGCV in adult kidney transplant recipients). Adult CMV D+/R− kidney transplant recipients (n=600) will be randomized 1:1 to receive either LET or VGCV starting within 7 days post-transplant and continuing through Week 28. Efficacy as measured by the proportion of participants with adjudicated CMV disease (see Section 4.2.1.2.1) through Week 52 post-transplant as well as safety in kidney transplant recipients will be evaluated. There are no P002 sites in Japan. Details of P002 study can be found in the accompanying IB. Two more clinical studies involving LET for HSCT patients are ongoing/being planned. 1) P040; a Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of LET prophylaxis when extended from 100 days to 200 days post-transplant in CMV R+ of an allogenic HSCT, and 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.

2.3 Benefit/Risk Assessment

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There are no hypotheses to be tested in this study.

In adult Japanese kidney transplant recipients who are organ donor (D) or organ recipient (R) seropositive (D+/R−, D+/R+ or D−/R+) for CMV:

Objectives	Endpoints
Primary	
◦ To evaluate the safety and tolerability of letermovir based on the proportion of participants with adverse events.	◦ Adverse events (AEs) ◦ Study drug discontinuations due to AEs
Secondary	
◦ To evaluate the efficacy of letermovir in prevention of CMV disease and infection, as measured by the proportion of participants with adjudicated CMV disease or participants who have undergone anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) through Week 28 and Week 52 post-transplant.	◦ Adjudicated CMV disease OR anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local)
◦ To evaluate the efficacy of letermovir in prevention of CMV disease, as measured by the proportion of participants with adjudicated CMV disease through Week 28 and Week 52 post-transplant.	◦ Adjudicated CMV disease
◦ To evaluate the efficacy of letermovir in prevention of CMV infection, as measured by the proportion of participants with quantifiable CMV DNAemia (central) through Week 28 and Week 52 post-transplant.	◦ Quantifiable CMV DNAemia (central)
◦ To evaluate the pharmacokinetics of letermovir in Japanese kidney transplant recipients.	◦ Pharmacokinetic endpoints (the plasma concentrations of LET, PK parameters, ie, Oral: AUC_{tau}, C_{trough}, C_{max}, T_{max}, CL_{ss}/F; IV: AUC_{tau}, C_{trough}, C_{eoi}, CL_{ss})

Objectives	Endpoints
Tertiary/Exploratory	
◦ To evaluate the proportion of patients experiencing allograft dysfunction and/or rejection through Week 28 and Week 52 post-transplant.	◦ Allograft dysfunction or rejection
◦ To evaluate the incidence of new onset diabetes mellitus after transplant (NODAT) through Week 28 and Week 52 post-transplant.	◦ NODAT
◦ To evaluate health outcomes through Week 28 and Week 52 post-transplant.	◦ Health outcomes (incidence of all-cause mortality, re-hospitalizations, opportunistic infections)
◦ To evaluate the antiviral resistance to letermovir in prophylaxis failures through Week 52 post-transplant.	◦ Antiviral resistance
◦ To explore the relationship between genetic variation and response to the prophylactic intervention administered, and mechanisms of disease. a. Variation across the human genome may be analyzed for association with clinical data collected in this study. b. Variation in the SLCO1B1 (OATP1B1) and UGT1A1 genes will also specifically be evaluated.	◦ Genetic analysis

4 STUDY DESIGN

4.1 Overall Design

This is a nonrandomized, single-arm, multi-site, open-label study to evaluate the safety, efficacy and pharmacokinetics of letermovir for the prevention of CMV infection and disease in adult Japanese kidney transplant recipients.

This study will be conducted in conformance with Good Clinical Practices (GCP). The definition of CMV disease is provided in Section 4.2.1.2.

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

Approximately 20 Japanese D+ and/or R+ kidney transplant recipients will be enrolled to receive LET within 7 days post-transplant. Of the 20 participants in total, at least 10 D+/R− kidney transplant recipients, who have the highest risk of developing CMV disease, will be enrolled. R+ (either D+/R+ or D–/R+) kidney transplant recipients, who are at intermediate risk of CMV disease, will be allowed to be enrolled at the investigators' discretion if the investigator considers the patient would benefit from 200 days of prophylaxis.

From Day 1 (day of allocation) through Week 28, all participants will receive:

- LET 480 mg once daily (QD) given orally (two 240 mg tablets), or, if the participant is receiving concomitant cyclosporin A (CsA), LET 240 mg (one 240 mg tablet) QD given orally.

The above assumes:

- Participants can tolerate swallowing and/or does not develop a condition that may interfere with the absorption of the oral formulation.

If participants are unable to tolerate swallowing and/or have a condition (eg, vomiting, diarrhea, or a malabsorptive condition) that may interfere with the absorption of the oral formulation at or after Day 1, then such participants can be initiated/switched to the IV formulation of LET. Participants not on concomitant CsA will receive 480 mg IV LET QD, while participants on concomitant CsA will receive 240 mg IV LET QD.

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

After completion of study therapy at Week 28, participants will continue to be followed for safety, efficacy, and diagnosis of CMV disease, and complete all remaining visits through Week 52. Participants who discontinue study medication early (ie, prior to Week 28) will complete all remaining treatment-period visits through Week 28, as well as all remaining visits through Week 52 as outlined in the SoA (Section 1.3) with the exception of study therapy administration, PK assessments, and study medication diary review. All scheduled study visits will be completed regardless of when cessation of study treatment occurs.

An independent Clinical Adjudication Committee (CAC) will be established for this study to adjudicate all potential CMV disease cases, as identified by site investigators or as otherwise described in the CAC charter (see Section 4.2.1.2.1 and Appendix 8).

4.2 Scientific Rationale for Study Design

Since the number of kidney transplants in Japan is extremely limited (around 1700 cases annually) [Japanese Society for Clinical Renal Transplantation, 2018], the P042 study is conducted as a nonrandomized, single-arm, multi-site, open-label study for a total of 20 D+/R−, D+/R+ or D−/R+ participants (with at least 10 being D+/R−) based on feasibility of enrollment.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

The safety and tolerability of LET will be assessed by a clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examination, 12 lead electrocardiograms (ECGs), and standard laboratory safety tests at appropriate timepoints, as specified in the SoA. AEs are evaluated and recorded according to Section 8.4. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

4.2.1.2 Efficacy Endpoints

The efficacy endpoints of the study (secondary endpoints) are:

- Adjudicated CMV disease or initiation of anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) through Week 28 and Week 52 post-transplant.
- Adjudicated CMV disease through Week 28 and Week 52 post-transplant.
- Quantifiable CMV DNAemia (central) through Week 28 and Week 52 post-transplant.

Following CMV prophylaxis with 200 days of VGCV in the non-Japanese D+/R− kidney transplant recipient population, the incidence rates of CMV disease and CMV DNAemia through Week 52 post-transplant have been described [Humar, A., et al 2010]. Currently, there is no universally accepted threshold of CMV DNA levels for therapy or treatment endpoints in the SOT recipient population [Kotton, C.N., et al, 2018].

For the Japanese D+/R− kidney transplant recipient population, 200 days of VGCV for CMV prophylaxis is recommended [Japanese Society for Clinical Renal Transplantation Guideline Work Group 2011; Addendum in 2015]. However, SOC for CMV management in the kidney transplant recipient population in Japan is anticipated to vary depending on sites and/or investigators. In many sites, kidney transplant recipients may not be started on VGCV prophylaxis following transplant and/or started on anti-CMV treatment at the time of onset of CMV disease. Instead, such kidney transplant recipients in Japan are serially monitored by the pp65 CMV antigen assay for post-transplant CMV infection regardless of whether prophylaxis or PET strategy is utilized for CMV management, and started on anti-CMV

treatment when CMV infection is detected. As for R+ kidney transplant recipient population, PET is recommended for the clinical strategy for preventing CMV disease in the Japanese guideline [Japanese Society for Clinical Renal Transplantation Guideline Work Group 2011; Addendum in 2015].

During the P042 study, the Sponsor anticipates that: 1) serial monitoring for CMV infection may occur as SOC in Japan during and after LET prophylaxis, ie, during study treatment and follow-up periods; and 2) detection of CMV infection at any time during the study may lead to cessation of LET prophylaxis (if during study treatment period) and initiation of anti-CMV treatment. Therefore, for the P042 study population, the incidence of CMV disease is expected to be lower than what was previously reported for the IMPACT study population (routine CMV monitoring was prohibited during study period in the IMPACT study unless as part of the management of an established CMV infection), ie, the kidney transplant recipients in the P042 study population with CMV infection are expected to be started on anti-CMV treatment prior to the clinical progression of CMV infection to CMV disease. Therefore, in addition to the clinical efficacy endpoints of the proportion of adjudicated CMV disease and the proportion of patients with quantifiable DNAemia (central) applied in the IMPACT study [Humar, A., et al 2010], the proportion of participants with adjudicated CMV disease or participants who have received anti-CMV treatment based on positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) will also be analyzed.

For this study, CMV infection, CMV disease, CMV end-organ disease, and CMV syndrome are as defined by the Disease Definitions Working Group of the CMV Drug Development Forum in 2016 [Ljungman, P., et al 2016].

CMV infection is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen.

CMV disease consists of the two following clinical definitions: 1) CMV end-organ disease; and 2) “probable CMV syndrome” (which will be termed “CMV syndrome” throughout this protocol).

- CMV end-organ disease (full definition in Appendix 8) may be further described by:
    - The specific type of end-organ disease (eg, pneumonia, gastrointestinal disease, or hepatitis); and
    - By categorization based on appropriate clinical signs/symptoms with detection/documentation of CMV by:
        - Proven CMV end-organ disease
        - Probable CMV end-organ disease
- CMV syndrome (full list of criteria and clinical definition in Appendix 8) requires detection of CMV in blood by virus isolation, rapid culture, antigenemia, or nucleic acid testing with at least two of the criteria, as outlined in Appendix 8.

4.2.1.2.1 CMV Based Assessments

CMV DNA Measurements (performed by the central laboratory)

"Quantifiable CMV DNAemia (central)" is included as a secondary endpoint in this study. In this study, CMV DNAemia (viral load) will be measured on plasma samples using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) assay, which will be performed by the central laboratory. The lower limit of quantification (LLOQ) for this assay is 137 IU/mL which is approximately 151 copies/mL (using a conversion factor of 1.1 copies/IU as per the assay package insert).

The CMV DNA levels in IU/mL will be reported as one of the following:

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

"Quantifiable CMV DNAemia (central)" is defined as any case with a numeric value or reported as ">910,000,000" and does not include reporting of polymerase chain reaction (PCR) results as "<137 not detected" or "<137 detected, not quantifiable". Additional details on CMV DNA PCR testing are described in Section 8.2.1.2.

CMV DNA Measurements and CMV antigenemia (performed locally)

In addition to central CMV DNA PCR testing at the timepoints indicated in the Study SoA (see Section 1.3), local CMV DNA PCR and/or CMV antigenemia testing may be conducted at the investigators' discretion per institutional standards (Section 4.2.1.2). Local CMV test results will be used to determine "anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local)" which is a component of a secondary endpoint in this study.

"Anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local)" is defined as initiation of approved anti-CMV agents based on at least one positive cell on CMV antigenemia and/or numeric value (not including the result of "Detected but not quantifiable") of CMV DNA PCR assay performed locally. Additional details on local CMV DNA PCR testing and CMV antigenemia are described in Section 8.2.1.2.

CMV Disease Assessments

In addition, all potential cases of CMV disease, as identified by site investigators or as otherwise described in the CAC charter, will be confirmed by an independent CAC. The CAC will review any available data (as documented in the CAC charter) for the participant,

including but not limited to clinical, laboratory, radiographic, and/or histopathological data, as well as the investigators' assessments from all potential cases of CMV disease as identified by site investigators throughout the study. The adjudication of cases by the CAC will take precedence over the investigator's assessment. Only cases that are adjudicated by the CAC as a "yes" to CMV disease ("adjudicated CMV disease") will be included in the efficacy endpoints.

Adjudication of CMV disease cases by an established CAC will standardize the CMV disease diagnosis for the secondary efficacy endpoints.

QuantiFERON-CMV Measurements

The development of CMV-specific T cell responses, which is the predominant adaptive immune response that confers protection against CMV [Manuel, O., et al 2013] [Abate, D., et al 2013] [Cantisan, S., et al 2013] [Fernandez-Ruiz, M., et al 2014], will be measured using the QuantiFERON-CMV assay at the timepoints indicated in the Study SoA (see Section 1.3). At each of these timepoints, the proportion of participants with positive QuantiFERON-CMV assay results will be correlated with the incidence of adjudicated CMV disease and/or participants who have undergone anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) through 52 weeks post-transplant and assessed as an exploratory endpoint.

The proportion of SOT patients (including kidney transplant recipients) who develop CMV-specific T cell responses following 3 to 6 months of VGCV prophylaxis has previously been reported [Manuel, O., et al 2013] [Abate, D., et al 2013] [Cantisan, S., et al 2013] [Fernandez-Ruiz, M., et al 2014] while the incidence of such immune response following LET prophylaxis in this patient population has not been previously studied. The Week 40 (ie, 3 months post prophylaxis) and Week 52 (ie, 6 months post prophylaxis) timepoints for this study are previously used in the VGCV prophylaxis reports. Moreover, there is preclinical evidence to suggest that treatment with LET is accompanied by the cytoplasmic accumulation of large amounts of subviral, noninfectious particles termed dense bodies (DBs) within CMV-infected cells [Goldner, T., et al 2011]. Since DBs are immunogenic and prime lymphocytes and neutralizing antibodies in mice, it may be speculated that the release of non-infectious, immunogenic DB during LET prophylaxis may facilitate antiviral immune response following immunosuppression in kidney transplant recipients and as measured by the QuantiFERON-CMV assay [Becke, S., et al 2010] [Goldner, T., et al 2011]. The anti-CMV response at Week 12 and Week 28 timepoints will determine whether such responses may be elicited during LET administration. The central laboratory based QuantiFERON-CMV assay results will not be shared with the respective site investigators.

4.2.1.2.2 New Onset Diabetes Mellitus After Transplant (NODAT)

NODAT is a standard clinical event to be monitored following kidney transplant and the incidence of NODAT is also included in the IMPACT study [Humar, A., et al 2010]. An increased risk of NODAT is considered one of the indirect effects resulting from CMV infection, along with others such as allograft rejection and opportunistic infections

(Section 2.1). As preventing CMV infection may then result in decreased incidence of NODAT, this will be evaluated as an efficacy endpoint.

Diabetes mellitus is defined according to the World Health Organization (WHO) and American Diabetes Association (ADA) as follows [Kidney Disease: Improving Global Outcomes Transplant Work Group 2009]:

1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.*

OR

2. Symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

OR

3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

NODAT is diabetes mellitus defined by the WHO and ADA that develops for the first time after kidney transplantation [Kidney Disease: Improving Global Outcomes Transplant Work Group 2009]. The incidence of NODAT is highest in the first 3 months after transplantation. The cumulative incidence of NODAT by the end of the first year has generally been found to be 10% - 30% in adult kidney transplant recipients receiving CsA or tacrolimus plus corticosteroids [Kidney Disease: Improving Global Outcomes Transplant Work Group 2009].

4.2.1.3 Pharmacokinetic Endpoints

Pharmacokinetic (PK) samples will be collected from all participants as described in the SoA (Section 1.3). The intensive and trough PK data will be used to characterize the PK of LET in Japanese kidney transplant recipients. Intensive PK data will be analyzed by non-compartment analysis and descriptive statistics of PK parameters (as shown in below) will be provided by treatment:

- Oral: AUC_{tau}, C_{trough}, C_{max}, T_{max}, CL_{ss}/F
- IV: AUC_{tau}, C_{trough}, C_{eoi}, CL_{ss}

Table 1 summarizes the requirements of trough PK and intensive PK collection during the study.

Table 1 Trough Pharmacokinetic and Intensive Pharmacokinetic Collection

	Trough PK – Pre-dose at Each Visit of Treatment Period	Week 1 Intensive PK	Additional Intensive PK
All participants	X	X	
Participants with dose formulation switch			X

IV = intravenous; PK = pharmacokinetics; PO = Orally

If Week 1 intensive PK is performed after PO therapy and the dose formulation is then switched from PO to IV, ALL participants who receive 6 or more consecutive days of IV therapy will have intensive PK.

If Week 1 intensive PK is performed after IV therapy and the dose formulation is then switched from IV to PO, participants who receive 6 or more consecutive days of PO therapy will have intensive PK if required sample collection is feasible.

No more than twice will intensive PK sampling be performed during the entire study for a single participant, regardless of how many times the dose formulation is switched during the study.

Details of PK sample collection is in Section 8.6.1.

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

In addition to studying variation across the human genome, variants in the SLCO1B1 (OATP1B1) and UGT1A1 genes will specifically be investigated for PK variability, as well as efficacy and safety.

4.2.1.5 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

This clinical study will evaluate:

- LET
    - 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 LET

LET 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.

LET has been safe and well tolerated in 31 Phase 1 studies in which participants received oral LET single doses ranging from 5 mg to 720 mg and multiple doses ranging from 40 mg QD to 720 mg twice daily (BID), or received IV LET 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), LET 240 mg QD, during an 84-day treatment period, was well tolerated with a safety profile similar to placebo.

In the Phase 2b dose-ranging study (P020) conducted in HSCT recipients, a dose response was observed. LET doses of 60 mg, 120 mg, or 240 mg, or placebo, were given once daily in 131 total participants. 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 LET (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 LET when compared to placebo. LET was generally well-tolerated at all three doses in P020.

Phase 1 studies demonstrated that co-dosing with CsA increases LET exposure. Further analyses using the Phase 2b study (P020) data indicated that exposure with the 240 mg QD dose of LET 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 LET 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 LET 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 Japanese participants [Marty, F. M., et al 2017]. Treatment with LET 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 LET compared to placebo. LET 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 LET group compared to the placebo group. All-cause mortality was substantially lower in the LET group compared to the placebo group through Week 24 and Week 48 post-transplant. LET 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 P042 study, the doses of LET that were previously used in the Phase 3 evaluation in HSCT recipients including Japanese participants will be used. Since the target of LET is the CMV viral terminase complex, considering the mechanism of action, the LET doses shown to be effective in the HSCT recipient population is anticipated to be effective in the SOT recipient population.

The IV formulation of LET contains the excipient hydroxypropyl betadex. Following precautions are noted in the LET label; “there is a possibility that worsening of renal function and, etc. by accumulation of the excipient hydroxypropyl-β-cyclodextrin in the IV Infusion may occur in patients with renal impairment, the duration of use with the IV Infusion should be kept to a minimum. Oral administration should be selected for patients for whom oral administration is possible.” Also, the effect of renal impairment on LET PK was evaluated in

participants with moderate (estimated glomerular filtration rate [eGFR] ≥30 to 59 mL/min/1.73 m^2) or severe renal impairment (eGFR <30 mL/min/1.73 m^2; actual range: 11.86-28.14 mL/min/1.73 m^2; Study P006) [Kropeit, D., et al 2017]. Based on the P006 study results, no dose adjustment is recommended for participants with moderate or severe renal impairment as is in the LET label [Japan Prescribing Information, PREVYMIS 2018]. For this study in renal transplant participants, the LET dose for IV formulation is selected as 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 at or after Day 1. Use of the IV formulation should generally be limited to 4 weeks or less in duration per participant.

4.3.2 Rationale for Dose Interval and Study Design

CMV prophylaxis has been associated with reductions in CMV disease, mortality, and graft rejection in high-risk patients [Humar, A., et al 2010] [Hodson, E. M., et al 2013] [Kalil, A. C., et al 2005] [Lowance, D., et al 1999]. The clinical benefit of CMV prophylaxis for 200 days (ie, 28 weeks) instead of 100 days (ie, 14 weeks) to decrease the incidence of CMV disease has been shown in the IMPACT study comparing VGCV prophylaxis for 200 days versus 100 days in kidney transplant recipients [Humar, A., et al 2010]. In this study, the incidence of CMV disease by 12 months post-transplant was 16.1% in the 200-day group compared to 36.8% in the 100-day group ($p<0.0001$). The relative and absolute risk reduction observed with prolonged prophylaxis (ie, 6 months) was 56% and 21%, respectively, which corresponds to a number needed to treat approximately 5 in order to prevent each case of CMV disease up to 12 months post-transplant [Humar, A., et al 2010]. Prolongation of prophylaxis to 6 months or longer has been proposed as a potential strategy to decrease the incidence of CMV disease in SOT recipients [Humar, A., et al 2010] [Doyle, A. M., et al 2006] [Valentine, V. G., et al 2008] [Schnitzler, M. A., et al 2003]; for this study, a post-transplant prophylaxis duration of approximately 28 weeks will be used as was done in the IMPACT study conducted in D+/R− kidney transplant recipients [Humar, A., et al 2010]. Duration of prophylaxis in R+ (either D+/R+ or D–/R+) kidney transplant recipients is noted in the oversea guideline [Kotton, C.N., et al 2018]; between 3 and 6 months of prophylaxis for the patients whose risk for CMV may be increased (eg, those on recent antilymphocyte therapy, desensitization) may be effective. Therefore, for this study, R+ kidney transplant recipients will be allowed to be enrolled at the investigators' discretion if the investigator considers the patient would benefit from 200 days of prophylaxis, and the safety and efficacy of 200 days dosing will be assessed in all participants. Participants will be followed through Week 52 to evaluate the incidence of late onset CMV disease after the conclusion of study medication.

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 (ie, the participant is unable to be contacted by the investigator).

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/clinical endpoints 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 due to insufficient compliance with the protocol, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male/Female Japanese participants with receipt of a kidney transplant of at least 18 years of age will be enrolled in this study.

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

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Meet either of the following recipient and/or donor CMV Immunoglobulin G (IgG) serostatus:

    a) Have a documented negative serostatus for CMV (ie, recipient CMV IgG seronegative [R−]) within 90 days prior to allocation. AND anticipate receiving an allograft kidney from a CMV IgG seropositive (D+) donor at the time of screening AND have received an allograft kidney from a documented D+ donor at the time of allocation.

    Note: A donor who is seropositive solely based on having received a CMV-seropositive transfusion immediately prior to organ donation is not considered to be a seropositive donor in this study.

    b) Have a documented positive serostatus for CMV (ie, recipient CMV IgG seropositive [R+]) AND the investigator considers the patient would benefit from 200 days of prophylaxis.

    Note: Either D+ or D– is allowed for donor serostatus (D+/R+ or D–/R+).

2. Anticipate receiving a primary or secondary allograft kidney at the time of screening AND have received a primary or secondary allograft kidney at the time of allocation.

3. Be within 0 (ie, day of transplantation) to 7 days (inclusive) post-kidney transplant at the time of allocation.

Demographics

4. Participant is a Japanese male or female from 18 years to any years of age inclusive, at the time of signing the informed consent.

   Note: Participant under 20 years of age should be provided written informed consent by legally acceptable representative.

Female Participants

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

   - Is not a woman of childbearing potential (WOCBP)

     OR

   - Is a WOCBP and using 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.

   - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) within 72 hours before the first dose of study intervention.

   - Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

6. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the main study without participating in FBR.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Received a previous solid organ transplant or HSCT.

   Note: Participants who have received a prior primary allograft kidney may be enrolled, provided that all other inclusion/exclusion criteria are met.

2. Is a multi-organ transplant recipient (eg, kidney-pancreas).
   Note: Double kidney transplant recipients (ie, transplant of two kidneys from the same donor to the same recipient simultaneously) will be excluded.

3. Has a history of CMV disease or suspected CMV disease within 6 months prior to allocation.

4. Positive results on CMV DNA PCR assay and/or CMV antigen test (if either/both tests are performed as local SOC) at any time between the completion of the transplant surgery and time of allocation.
   Note: Positive result on CMV DNA PCR is defined as with numeric value of CMV DNA. Positive result on CMV antigenemia is defined as with at least one positive cell.

5. Has suspected or known hypersensitivity to active or inactive ingredients of LET formulations.

6. Is on dialysis or plasmapheresis at the time of allocation.
   Note: For the purposes of this protocol, dialysis includes hemofiltration. Participant who: (1) has had dialysis or plasmapheresis within 7 days (inclusive) post-transplant but is not on dialysis or plasmapheresis at the time of allocation; and (2) is expected to remain off dialysis or plasmapheresis may be enrolled, provided that all other inclusion/exclusion criteria are met.

7. Has post-transplant renal function of creatinine clearance (CrCl) ≤10 mL/min at allocation (measured locally). For this exclusion criterion, CrCl will be calculated using the Cockcroft-Gault equation using the most recently obtained and available serum creatinine value collected within 3 calendar days prior to and including the day of allocation and after the conclusion of any clinically warranted (at the discretion of the investigator) post-transplant dialysis or plasmapheresis.
   Note: Participants who meet this exclusion criterion at screening may, at the discretion of the investigator, have one repeat testing done within 3 days prior to allocation. If the repeat value meets this exclusion criterion again, such participants may NOT continue in the screening/allocation process. Only the laboratory test with specific out-of-range value (and not the entire laboratory panel) should be repeated.

CrCl (Males) = $\frac{\text{(weight in kg) (140 – age)}}{\text{(72) (creatinine in mg/dL)}}$

CrCl (Females) = 0.85 × male value (ie, the value obtained with formula above)

8. Has Child-Pugh Class C severe hepatic insufficiency (Appendix 9) at screening.

   Note: 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.

9. Has both moderate hepatic insufficiency AND moderate-to-severe renal insufficiency at screening.
   Note: Moderate hepatic insufficiency is defined as Child-Pugh Class B (see Note for exclusion criteria 8 above and Appendix 9); moderate-to-severe renal insufficiency is defined as CrCl <50 mL/min, as calculated by the Cockcroft-Gault equation (as above), respectively.

10. Has any uncontrolled infection on the day of allocation.

11. Has documented positive results for human immunodeficiency virus antibody (HIV-Ab) test at any time prior to allocation, or for hepatitis C virus antibody (HCV-Ab) and with detectable HCV RNA within 90 days prior to allocation or hepatitis B surface antigen (HBsAg) within 90 days prior to allocation.

12. Requires mechanical ventilation, or is hemodynamically unstable, at the time of allocation.

13. Has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or carcinoma in situ; or is under evaluation for other active or suspected malignancy.

14. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or put the participant 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.

15. Has exclusionary laboratory value at the screening visit, as listed in Table 2.

Table 2 Laboratory Exclusion Criteria

Laboratory Assessment	Exclusionary Value
Hemoglobin	<8 g/dL
Platelets	<25,000 cells/μL
Total bilirubin	>2.5 x ULN
AST	>5 x ULN
ALT	>5 x ULN
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal	

Prior/Concomitant Therapy

16. Has received within 30 days prior to allocation or plans to receive during the study any of the following anti-CMV IgG antibody treatment or anti-CMV drug therapy including:

    a. CMV immune globulin
    b. Any investigational CMV antiviral agent/biologic therapy.

17. Has received any dose of LET prior to allocation.

18. Has received within 7 days prior to allocation or plans to receive during the study any of the following anti-CMV drug therapy including:

    a. GCV
    b. VGCV
    c. Foscarnet
    d. Acyclovir (at doses >3200 mg PO per day or >25 mg/kg IV per day)
    e. Valacyclovir (at doses >3000 mg PO per day)
    f. Famciclovir (at doses >1500 mg PO per day)

19. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence.

20. Is taking or plans to take any of the prohibited medications listed in the protocol (see Section 6.5.1).

Prior/Concurrent Clinical Study Experience

21. 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 (excluding monoclonal antibodies), whichever is longer, of initial dosing on this study. Participants previously treated with an investigational monoclonal antibody will be eligible to participate after a 150-day washout period.
    Note: Investigational regimens involving combinations of approved agents are not permitted. Other non-interventional or other observational studies are allowed.

22. Has previously participated in this study or any other study involving LET.

23. 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 the course of this study.

Other Exclusions

24. Is pregnant or expecting to conceive, is breastfeeding, or plans to breastfeed from the time of consent through at least 28 days following cessation of study therapy.

25. Is expecting to donate eggs starting from the time of consent through at least 28 days following cessation of study therapy.

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

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

The oral formulation of LET demonstrates no clinically significant food effect, thus participants may take the study drug orally without regard to food. However, there may be restrictions with other non-study 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 (eg, participants who are taking CsA concomitantly with LET must avoid consumption of grapefruit and grapefruit juice).

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

A participant who discontinues from study 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 intervention(s) to be used in this study are outlined in Table 3 (PO) and Table 4 (IV).

In this study, approximately 20 participants will be enrolled to receive LET once a day from the day of enrollment (Day 1, within 7 days post-transplant) through 28 weeks (~200 days) post-transplant. Participants without concomitant CsA use will be dosed 480 mg (two 240 mg tablets) once daily and participants with concomitant CsA use will be dosed 240 mg (one 240 mg tablet) once daily.

For participants who cannot tolerate swallowing and/or develop a condition that may interfere with the absorption of the oral formulation at or after Day 1, study therapy can be initiated/switched to the IV formulation. Simultaneous use of IV and oral study therapy is **not** allowed. 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 IV formulation should be switched to oral study therapy (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 3 Study Therapy – Oral (Tablet) Formulation

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
LET (for participants on CsA)	240 mg	Once daily	Oral	QD from Day 1 to Week 28	Experimental	IMP	Sponsor
LET (for participants not on CsA)	480 mg (two 240-mg tablets)	Once daily	Oral	QD from Day 1 to Week 28	Experimental	IMP	Sponsor

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission.

LET = letermovir; CsA = Cyclosporin A; QD = Once daily

Table 4 Study Therapy – Intravenous Formulation

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
LET (for participants on CsA)	240 mg	Once daily	IV	QD from Day 1 to Week 28 [b]	Experimental	IMP	Sponsor
LET (for participants not on CsA)	480 mg	Once daily	IV	QD from Day 1 to Week 28 [b]	Experimental	IMP	Sponsor

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission.

LET = letermovir; CsA = Cyclosporin A; IV = intravenous; QD = Once daily

a: LET IV formulation dosing volume is 250 mL and duration of infusion will be 60 minutes. LET IV will be provided as a sterile liquid concentrate for dilution (20 mg/mL), one vial to be used for the 240-mg dose and two vials for the 480-mg dose.

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

All supplies indicated in Table 3 and Table 4 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.1.1 Medical Devices

There are no medical devices to be used in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

Intervention allocation will be stratified according to the following factors:

1. CMV seropositivity subgroups (D+/R– and R+).

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.

Compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the time periods specified by this protocol. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination 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.

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.

Since this list 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 when appropriate.

6.5.1 Prohibited Medication

Letermovir is a substrate of OATP1B1/3, a time-dependent inhibitor of CYP3A, and inhibits breast cancer resistance protein (BCRP) and OATP1B1/3. Furthermore, letermovir may induce CYP2C9 and CYP2C19. Medications/therapies that are prohibited are outlined as follows.

The following medications/therapies are prohibited during treatment period and all of follow-up period.

- Antiviral drugs or therapies for prevention/treatment of CMV, including but not limited to:
  - letermovir that is not part of study intervention
  - ganciclovir
  - valganciclovir
  - foscarnet
  - acyclovir (at doses >3200 mg PO per day or >25 mg/kg IV per day)
  - valacyclovir (at doses >3000 mg PO per day)
  - famciclovir (at doses >1500 mg PO per day)
  - any investigational CMV antiviral agent/biologic therapy, including CMV vaccines or CMV hyper-immune globulin

  Note: these agents may be used for other indications while participants are on study therapy and all of follow-up period [eg, foscarnet for the treatment of human herpes virus 6 (HHV 6) or acyclovir for treatment of disseminated zoster]

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

- Investigational Agents: Unapproved investigational agents or investigational regimens involving combinations of *approved* agents are not permitted.

- CYP3A substrates with narrow therapeutic range (NTR), including but not limited to:
  - Pimozide: Concomitant administration of LET may result in increased concentrations of pimozide due to inhibition of CYP3A by LET, which may lead to QT prolongation and ventricular arrhythmia.
  - Ergot alkaloids: Concomitant administration of LET may result in increased concentration of ergot alkaloids (eg, ergotamine and dihydroergotamine) due to inhibition of CYP3A by LET, which may lead to ergotism.
- HMG-CoA reductase inhibitors (statins):
  - Simvastatin and pitavastatin: Concomitant administration of LET may result in increased simvastatin or pitavastatin concentrations, which may lead to myopathy.
- Enzyme and Transporter Inducers:
  - Strong inducers, such as rifampicin, phenytoin, carbamazepine, St John's wort (Hypericum perforatum), rifabutin and phenobarbital: Concomitant administration with LET may result in decreased concentration of LET, which may lead to decreased efficacy.
  - Moderate inducers, such as modafinil and bosentan: Concomitant administration with LET may result in decreased concentration of LET, which may lead to decreased efficacy.
- Everolimus when LET is co-administered with CsA: Co-administration of everolimus with LET and CsA may result in significantly increased everolimus concentrations due to CYP3A inhibition (Note: see Section 6.5.2 for co-administration of LET with everolimus).

It should be noted that the magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when LET is co-administered with CsA. Please also consult current prescribing information for CsA and other co-administered medications.

6.5.2 Medications/Therapies to be Administered with Caution

The following medications/therapies are allowed when coadministered with LET, but should be used with clinical monitoring for AEs related to these agents and/or drug level monitoring of these agents.

- **CYP3A substrates**:
  - Co-administration of LET with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates (eg, fentanyl, quinidine and midazolam). Therefore, frequent

monitoring for adverse reactions related to these agents is recommended during co-administration.

- Substrates of CYP3A with NTR (examples given below; please also consult current prescribing information for monitoring and dosing these products with inhibitors of CYP3A); dose adjustment of CYP3A substrates with NTR may be needed.

  - CsA: Co administration of LET with CsA increases CsA concentrations. Frequent monitoring of CsA whole blood concentrations should be performed during and at discontinuation of LET and the dose of CsA adjusted as appropriate.

  - Sirolimus: Co-administration of LET with sirolimus increases concentrations of sirolimus. Frequent monitoring of sirolimus whole blood concentrations should be performed during and at discontinuation of LET and the dose of sirolimus adjusted as appropriate.

  - Tacrolimus: Co-administration of LET with tacrolimus increases tacrolimus concentrations. Frequent monitoring of tacrolimus whole blood concentrations should be performed during and at discontinuation of LET and the dose of tacrolimus adjusted as appropriate.

  - Everolimus: Co-administration of LET with everolimus may increase everolimus concentrations. Frequent monitoring of everolimus blood concentrations should be performed during and at discontinuation of LET and the dose of everolimus adjusted accordingly. The administration of everolimus when LET is co-administered with CsA is prohibited (see Section 6.5.1).

- **Substrates of OATP1B1/3 and/or CYP3A:**

  - Statins:

    - Atorvastatin: Co-administration of LET with atorvastatin increases concentrations of atorvastatin. Monitoring for statin-associated adverse reactions (eg, myopathy) is recommended during co-administration.

    - Fluvastatin, rosuvastatin or pravastatin: Co-administration of LET with these drugs increases concentrations of these drugs. Monitoring for statin-associated adverse reactions (eg, myopathy) is recommended during co-administration.

- **Substrates of CYP2C9 and CYP2C19:**

  - Voriconazole: Co-administration of LET with voriconazole decreases the plasma concentrations of voriconazole likely due to induction of CYP2C9

and/or 2C19. If concomitant administration is necessary, close monitoring for reduced effectiveness of voriconazole is recommended.

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

6.5.3 Rescue Medications and Supportive Care

In the event of CMV disease (suspected or confirmed by the investigator) during the study therapy period (ie, prior to completion or early discontinuation of study therapy) or a clinical decision by the investigator to initiate anti-CMV treatment based on positive results on locally performed CMV DNA PCR or CMV antigenemia, study therapy will be discontinued (See Section 8.12.5) and the participant may be treated according to the local SOC (outside the context of the study). In this setting, any of the prohibited anti-CMV medications (as outlined in Section 6.5.1) may be used.

6.6 Dose Modification (Escalation/Titration/Other)

Please see Section 4.3.1 for LET dose to be used with or without co-administered CsA and Section 8.1.9.2 for information regarding dose modifications if CsA is initiated or discontinued during study therapy treatment period.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.4.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10 and Section 8.12.5.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has confirmed or suspected CMV disease and/or CMV infection that requires anti-CMV treatment as determined by the investigator (Section 4.2.1.2).
- The participant has a confirmed positive pregnancy test.
- An investigator feels it is in the best interest of the participant to discontinue.
- An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is greater than or equal to 3 × upper limit of normal (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 one of the following:

  - 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).

    Note: 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.

The participant **may** be discontinued from study intervention for any of the following reasons but continue to be monitored in the study:

- Any AE/SAE assessed by the investigator as 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, placed the participant at unnecessary risk from continued administration of study intervention.

Participants who interrupt (see Section 8.12.5.1) or discontinue study therapy prior to Week 28 because they are confirmed or suspected of developing CMV disease or CMV infection that require anti-CMV treatment must complete a CMV Infection Visit (Sections 1.3 [SoA] and 8.12.5.1). A CMV Infection Visit may be performed at any time when one or more criteria for the CMV Infection Visit (Section 8.12.5.1) is fulfilled. If the investigator decides to conduct a CMV Infection Visit at a scheduled study visit, then the procedures for a CMV Infection Visit (if the participant is still on study therapy) should also be performed at the regular study visit. It is very important to ensure that all procedures, as outlined in the Study SoA (Section 1.3), are performed at the CMV Infection Visit immediately prior to the initiation of treatment of CMV infection/disease. Most importantly, a confirmatory plasma sample for CMV DNA PCR testing, a plasma sample for CMV viral resistance testing (note: once the CMV Infection Visit occurs, another plasma sample for CMV viral resistance testing should be collected at the next scheduled visit; see Section 8.2.2), and blood sample for CMV-specific T cell responses using the QuantiFERON-CMV assay should be collected at this visit and sent to the central laboratory. Thereafter, the participant should be treated according to the local SOC (outside the context of the study). These participants will complete all remaining treatment-period scheduled visits through Week 28, as well as all remaining scheduled visits through Week 52, as outlined in the SoA (Section 1.3). All scheduled study visits will be completed regardless of when cessation of study treatment occurs. All specified procedures through Week 28 will be completed for these participants with the exception of study therapy administration, PK assessments, and study medication diary review.

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

Discontinuation from study intervention is “permanent.” Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

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, as well as specific details regarding withdrawal from future biomedical research, 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 or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 329.5 mL (See Appendix 10). When a participant repeats CMV Infection Visit and/or Early Discontinuation Visit, the amount of blood may exceed the maximum amount.

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 each their legally acceptable representative) prior to participating in a clinical study or FBR. 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 consent form should be given to the participant 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.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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 on Day 1 (allocation).

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/randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before first dose of study medication.

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 administered for treatment of CMV disease or for initiation of anti-CMV treatment and all drug/biologic therapies used to prevent/treat acute and/or chronic rejection should be recorded at every visit through Week 52. During the follow-up period through Week 52, concomitant medication review and collection is limited to the above and all antimicrobials (antibacterials, antifungals, antiparasite agents, and antivirals), oral hypoglycemic agents, insulin, granulocyte colony-stimulating factor (G-CSF), and immunosuppressant agents.

8.1.6 Kidney Transplant/Dialysis Details Review

All relevant data about the kidney transplant will be collected on Day 1 (at allocation). This includes details regarding the donor and recipient CMV IgG serostatus, transplant type (donation from deceased or living donor [living related or living unrelated as determined by the site]), the ex-vivo time, the date and the duration of the transplant surgery, and any anti lymphocyte therapy prior to transplant.

Details regarding each dialysis or plasmapheresis session occurring between transplant and end of study will be collected.

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 prior to intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used 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/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.9 Study Intervention Administration

The first dose of study treatment will be administered at the trial site on Day 1 after allocation. Subsequent oral dosing will be performed by the participant.

For participants who develop a condition that interferes with their ability to swallow, or a condition that interferes with the absorption of the oral formulation (eg, vomiting, diarrhea,

or a malabsorptive condition), a LET IV formulation is available for those participants. The LET IV formulation dosing volume will be 250 mL and the duration of infusion will be 60 minutes. The infusion will be administered through a sterile in-line filter. Refer to the Pharmacy Manual for details on the filters that may be used. 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 8.12.5.1). 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 at approximately the same time each day for the duration of the study (ie, once daily for LET). Tablets are to be swallowed whole (ie, no crushing or chewing is allowed). Study intervention may be taken 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 of study medication, the missed dose should be taken 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.

Participants with post-allocation CrCl ≤10 mL/min or who require dialysis or plasmapheresis after allocation will have their study medication interrupted, but could resume medication once CrCl increases to >10 mL/min and dialysis or plasmapheresis is no longer required provided they had not missed >7 consecutive days of study medication.

8.1.9.2 Dose Modifications when LET is Co-administered with CsA

Participants who are not on CsA will receive LET 480 mg QD given orally (two 240 mg tablets). Participants who are receiving concomitant CsA will receive oral formulation of LET 240 mg QD. Participants requiring IV formulation of LET who are not on CsA will receive 480 mg QD of IV LET. Participants requiring the IV formulation of LET who are on concomitant CsA will receive 240 mg QD of IV LET (Section 6.1).

If CsA is initiated after starting study intervention at an oral dose of LET 480 mg QD, the next dose of oral LET (administered up to 24 hours later) should be adjusted to 240 mg QD. If CsA is initiated after starting study intervention at an IV dose of LET 480 mg QD, the dose of IV LET (next administered up to 24 hours later and with continued need for IV formulation of LET) should be adjusted to 240 mg QD.

If CsA is discontinued during the study intervention period for more than 3 consecutive days, the dose of LET (next administered up to 24 hours later) should be increased from 240 mg to 480 mg QD.

8.1.9.3 Study Medication Diary and Recording the Study Intervention

For participants receiving oral tablets, 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 subject'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 prior to 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 8.12.4.

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

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

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

8.1.12 Domiciling

For participants who will undergo intensive PK sampling, the investigator should make arrangements such that all PK sampling at specified timepoints (ie, up to the last scheduled timepoint of 24 hours post-dose) will be performed as scheduled.

8.1.13 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 CMV Disease/Infection Assessment

8.2.1.1 Assessment of CMV Disease

CMV disease will be assessed at every visit from screening through Week 52. Diagnostic criteria for the evaluation of CMV disease are outlined in Appendix 8. If CMV Disease is suspected and anti-CMV therapy is started, site should perform the CMV Infection Visit instead of the scheduled visit assessments (see Sections 1.3 [SoA] and 8.12.5.1) 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.

8.2.1.2 Assessment of CMV Infection

Protocol-specified CMV DNA PCR assay

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

Protocol-specified CMV DNA PCR samples will be drawn at prespecified clinical visits: at allocation, Week 2, and Week 4; thereafter, samples must be collected on a monthly basis up to Week 52 and sent to the **central laboratory**, as indicated in the Study SoA (Section 1.3). The central laboratory CMV DNA PCR results will not be provided to the investigator.

Central laboratory based CMV DNA levels will be retrospectively analyzed at the end of the study.

Locally performed CMV DNA PCR assay or CMV antigenemia assay

In this study, the monitoring of CMV DNA levels or CMV antigenemia for the clinical management of participants may be performed locally at the discretion of the site investigator and/or clinical management team. When the local CMV DNA or antigenemia testing is conducted, every effort should be made to draw samples on the same day as the central testing. The protocol-specified CMV DNA PCR assay sample should be collected per protocol even if the local CMV DNA PCR or CMV antigenemia sample is drawn at the same visit. When a CMV DNA level and/or antigenemia is measured locally, it is mandatory that the results of locally performed CMV DNA PCR assay or antigenemia is entered to the CRF. There is no protocol-specified threshold for stopping CMV prophylaxis (if applicable) and initiating anti-CMV treatment.

If a clinical decision is made by the investigator to start anti-CMV treatment based on positive results on locally performed CMV DNA PCR or CMV antigenemia, a CMV Infection Visit will be completed prior to initiating anti-CMV treatment.

Note: It is mandatory to collect a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory **immediately prior to** (ie, on the day of) initiating anti-CMV treatment. 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 initiation of anti-CMV treatment (preferably within 48-72 hours).

Locally performed CMV DNA PCR assay or CMV antigenemia assay results will be retrospectively analyzed at the end of the study.

8.2.2 CMV Viral Resistance Testing

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

CMV viral resistance can contribute to clinical failure, ie, development of CMV infection/disease, during LET prophylaxis. LET resistance mutations in the CMV UL56, UL89 and UL51 genes (which encode subunits of the CMV DNA terminase complex) have been identified in *in vitro* viral cultures and UL56 mutations have been detected in participants who received LET and experienced virologic breakthrough.

To better understand the impact of genotypic variants on the susceptibility of CMV to LET, CMV viral resistance testing will be performed using plasma derived from blood collected at the CMV Infection Visit (and the following visit if applicable) from participants if any of the following occurs: (1) any discontinuation of study treatment in response to suspected or confirmed CMV disease; (2) any discontinuation of study treatment and initiation of anti-CMV treatment; or (3) initiation of anti-CMV treatment during the follow-up period (see Section 1.3). Once the CMV Infection Visit occurs, another plasma sample for CMV viral resistance testing should be collected at the next scheduled visit. Among these participants, a final sample for CMV viral resistance testing will also be collected at Week 52. Plasma samples may also be evaluated for the presence of known VGCV resistance mutations or other newly identified CMV mutations associated with LET resistance.

Analysis of genotypic variant will entail a variety of techniques that may include population sequencing and/or next generation sequencing. Additionally, phenotyping by marker transfer and investigational assays may be employed to distinguish LET resistance mutations from variants that have no impact on susceptibility to LET. CMV viral resistance testing may also be performed on leftover samples from other study-related testing.

8.2.3 CMV Serology (IgG) Testing

For each participant, the conduct of CMV serology (IgG) testing used at the site to determine the recipient CMV serostatus as part of pre-transplant evaluation (ie, within 90 days of allocation and/or as routine pre-transplant clinical management) will be as per local SOC for kidney transplantation recipients. The CMV serology assay for the kidney donor is expected to be performed at the medical facility at which the organ is harvested from the donor and as

per local SOC for the assessment of the kidney donor. Available CMV serology (IgG) testing data for the kidney donor and recipient will be obtained from the participant's chart.

8.2.4 QuantiFERON-CMV Assay

CMV-specific T-cell responses will be measured using the QuantiFERON-CMV assay [Becke, S., et al 2010] [Goldner, T., et al 2011] at various time points through Week 52 post-transplant using plasma samples. The central laboratory based QuantiFERON-CMV assay results will not be shared with the respective site investigators.

8.2.5 New Onset Diabetes Mellitus After Transplant (NODAT)

Participants developing NODAT (as identified by the site and also as identified by a confirmatory analysis) will be analyzed (Section 9). Site determination of participants with NODAT will be the primary method of identifying participants with NODAT and the site will identify and document which of the three WHO/ADA criteria for diabetes mellitus (See Section 4.2.1.2.2) and an additional category - "other" as identified and annotated by the investigator - has been fulfilled. Among participants identified by the site as developing NODAT, concomitant medications used during the study will be reviewed for use of insulin or an oral hypoglycemic agent between Week 4 and Week 52 to determine the method of NODAT management used by the site during the study [Bayer, N. D., et al 2010].

A confirmatory analysis for NODAT will be performed on the participants identified by the investigator as developing NODAT during the study as well as screening for cases of NODAT not identified by the investigator by identifying participants who fulfill one or more of the following:

1. Fasting blood glucose of ≥126 mg/dL (if available/specified as fasting blood glucose, since the protocol does not require that blood samples for chemistries be collected after fasting; it is expected that participants who fulfill the WHO/ADA NODAT Criterion 1, see Section 4.2.1.2.2, will also fulfill this confirmatory criterion).

AND/OR

2. AE of diabetes mellitus (for those who developed this AE during the AE reporting period).

AND/OR

3. Use of one or more hypoglycemic agents after allocation (ie, such hypoglycemic agents that are not listed as prior medications and newly identified as a concomitant medication during the study).

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 10.10 (Appendix 10).

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator as per institutional standard at the screening visit, Day 1 (allocation), and Week 28.

After Day 1 (allocation), the physical examination does not need to be performed at every visit except for Week 28; a targeted physical examination should be performed only if a participant has any complaints. The timing of physical examinations is indicated in the Study SoA (Section 1.3).

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

8.3.2 Vital Signs

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

- Pulse rate, blood pressure, and body temperature (oral preferred; see below).

  Note: Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, or axillary temperatures may be taken.

- Participants should be resting for at least 5 minutes prior to measurement of vital signs

8.3.3 Electrocardiograms

- Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

  Note: ECG will be performed if CMV Infection Visit or Early Discontinuation Visit will occur at Week 28.

- Participants should be resting for at least 10 minutes prior to having ECG readings obtained.

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

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

8.3.5 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 local (or central) 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 central or local laboratory parameters (total bilirubin, albumin, and INR) obtained at the corresponding scheduled study visit, or up to four weeks 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).

8.3.6 Confirmation of Contraception (WOCBP only)

Throughout the screening and treatment periods, precaution must be taken to avoid pregnancy in WOCBP. Confirmation must be obtained and documented by site personnel that WOCBP are using acceptable methods of contraception (see Appendix 5). This assessment must be documented in the participant's study chart at each specified visit.

8.3.7 Adverse Events Monitoring

Adverse event monitoring will include the collection of all AEs and SAEs from the time informed consent is signed through 14 days following the last dose of study treatment in all participants. Thereafter, any SAEs related to study medication will be collected through Week 52.

Refer to Section 8.4 for further details.

Infusion-Site Adverse Events for Participants Administered IV Study Intervention

Safety monitoring of infusion-site AEs will be performed by the evaluation of the site of infusion during and at the end of IV study intervention. Events will be entered on the AEs electronic case report form (eCRF).

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up 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/randomization, 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/randomization through 14 days following cessation of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

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

Investigators are not obligated to actively seek 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 he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (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
Serious Adverse Event (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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (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 randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

Efficacy endpoints (Health Outcomes) including re-hospitalizations (including rehospitalizations for CMV infection/disease), all-cause mortality, NODAT, biopsy-proven acute renal graft rejections, graft loss, use of G-CSF and select OIs (see Section 8.11 for a complete list) must be collected throughout the study (ie, during both treatment and follow-up). From the time of allocation, through 14 days following cessation of treatment, these events must be reported as described in Section 8.4.1. Efficacy endpoints (Health Outcomes) that occur after 14 days following cessation of treatment must continue to be assessed for seriousness and causality, however, they must only be reported within 24 hours as AEs if they are assessed as serious and there is evidence to suggest a causal relationship between the drug and the AE.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.5 Treatment of Overdose

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

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

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

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma Letermovir

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual. PK samples should not be collected in participants after discontinuation of study intervention.

Blood collection for trough PK (all participants)

Plasma samples for trough PK will be collected in all participants. A single sample per subject will be collected pre-dose (within 0-2 hours prior to dose) at each visit of the treatment period and at CMV Infection/early discontinuation visit (if during treatment period).

Blood collection for Week 1 intensive PK (all participants)

Plasma samples for Week 1 intensive PK will be collected at the following timepoints at any time between Study Day 6-10, IF the participant is treated with the same dose formulation (IV or PO) between Day 1 and the day of Week 1 intensive PK:

- Pre dose (within 0-2 hours prior to dose)
- 1 hour (± 10 min) following oral administration (or within 10 min after infusion completion, when given IV)
- 2.5 hours following oral/start of IV administration (± 30 min)
- 5 hours following oral/start of IV administration (± 30 min)
- 8 hours following oral/start of IV administration (range of 6-10 hours)
- 24 hours following oral/ start of IV administration (range of 22-24 hours; 0-2 hours prior to next day's dose)

If there is a switch in dose formulation (IV or PO) between Day 1 and the day of Week 1 intensive PK, Week 1 intensive PK will be performed on any day starting from the 6^{th} consecutive days of IV or PO therapy until the 10^{th} day after dose formulation switch (prior to and after the study dose on 6^{th} -10^{th} day after dose formulation switch). In this case, Week 1 intensive PK may be performed beyond Study Day 6-10.

Blood collection for additional intensive PK (participants with dose formulation switch)

Additionally, plasma samples for intensive PK will be collected for participants with dose formulation switch.

<Dose formulation switch from PO to IV>

If Week 1 intensive PK is performed after 6 or more consecutive days of PO therapy and the dose formulation is then switched from PO to IV, ALL participants who receives 6 or more consecutive days of IV dosing will have additional intensive PK. No more than ONCE during the entire study, regardless of how many times the IV therapy criterion is fulfilled during the study. The timing of the intensive PK collection will be on any day starting from the 6th consecutive day of IV therapy until the 10th day after switched to IV formulation at the following timepoints prior to and after start of study medication infusion:

- Pre dose (within 0-2 hours prior to dose)
- 1 hour (ie, within 10 min after infusion completion)
- 2.5 hours following the start of IV administration (± 30 min)
- 5 hours following the start of IV administration (± 30 min)
- 8 hours following the start of IV administration (range of 6-10 hours)
- 24 hours following the start of IV administration (range of 22-24 hours; 0-2 hours prior to next day's dose)

<Dose formulation switch from IV to PO >

If Week 1 intensive PK is performed after 6 or more consecutive days of IV therapy and the dose formulation is switched from IV to PO, participants who receives 6 or more consecutive days of PO dosing will have additional intensive PK, no more than ONCE during the entire study. Additional intensive PK after 6 or more consecutive days of PO therapy will be performed if required sample collection is feasible (eg, the participant is in the hospital). The timing of the intensive PK collection will be on any day starting from the 6th consecutive day of PO therapy until the 10th day after switched to PO formulation at the following timepoints prior to and after start of study medication:

- Pre dose (within 0-2 hours prior to dose)
- 1 hour (± 10 min) following oral administration
- 2.5 hours following oral administration (± 30 min)
- 5 hours following oral administration (± 30 min)
- 8 hours following oral administration (range of 6-10 hours)
- 24 hours following oral administration (range of 22-24 hours; 0-2 hours prior to next day's dose)

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- DNA for future research
- Leftover main study plasma from CMV DNA PCR stored for future research
- Leftover main study plasma from CMV viral resistance stored for future research

8.9 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for SLCO1B1 (OATP1B1) and UGT1A1 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to SLCO1B1 (OATP1B1) and UGT1A1. Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Health Outcomes Assessment

Health Outcomes assessed for this study will include collection of re-hospitalizations (including re-hospitalizations for CMV infection/disease), all-cause mortality, NODAT, select OIs, biopsy-proven acute renal graft rejections, graft loss, and use of G-CSF. These outcomes will be collected via electronic CRF as described in the SoA (Section 1.3). Select OIs [Kidney Disease: Improving Global Outcomes Transplant Work Group 2009] [Trofe-Clark, J. and Sawinski, D. 2016] are as follows:

- *Pneumocystis jirovecii* pneumonia
- BK virus infection
- Human polyomavirus (non-BK virus) infection
- HSV infection (including superficial, eg, oral HSV infection, and systemic HSV infection)

- VZV infection (including primary varicella zoster infection and herpes zoster [including uncomplicated and disseminated forms])
- Oral candidiasis
- Candidiasis (ie, non-oral Candida infection)
- *Mycobacterium tuberculosis* infection

8.12 Visit Requirements

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

8.12.1 Screening

Screening of potentially eligible participants may begin on as early as 1 day before transplantation for participants receiving a kidney from a deceased donor and up to 14 days prior to (including the day of transplantation [ie, prior to transplantation]) transplantation for participants receiving a kidney from a living donor. All screening procedures listed under Visit 1 of the Study SoA (Section 1.3) will be performed and must be completed by one day prior to Day 1. Participants will be allocated within 7 days post-transplant. The informed consent must be obtained before any study-specific procedure is performed. It is acceptable that the date of informed consent administration is earlier than the day screening procedures are performed. However, once informed consent is obtained, AE reporting must be conducted according to Section 8.3.7.

Potential participants will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as described in Sections 5.1 and 5.2. The investigator will discuss with each potential participant the nature of the study and its requirements/restrictions. All screening procedures listed under Visit 1 of the Study SoA (Section 1.3) will be performed.

Participants will be instructed about the restrictions for concomitant medications, as noted in Section 6.5. WOCBP participants will be instructed that they are required to use birth control, as described in Appendix 5, starting from the time of consent through 28 days after the last dose of study intervention.

For screening purposes, values from the participant's chart within 14 days prior to screening for required chemistry, hematology, coagulation, and urinalysis tests are acceptable. If not available, this testing may be performed by the central laboratory or locally per SOC (see Appendix 2).

HIV antibody test results documented at any time prior to allocation of the participant will be acceptable; a copy of this HIV report must be available (See Exclusion Criterion 11 in Section 5.2). If documentation of a previous HIV test is not available, the HIV antibody test must be conducted using the central or local laboratory. Hepatitis B and hepatitis C

screening should only be performed if not previously documented within the last 90 days. If HCV-Ab is positive, HCV RNA PCR results should be provided (or, if not available, HCV RNA PCR testing will be performed by the central or local laboratory).

On the day of allocation, eligibility for enrollment into the study should be confirmed.

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

Rescreening

Those participants who meet any of the laboratory exclusion criteria in Table 2 and/or Child-Pugh classification in Exclusion Criterion 9 at screening or whose kidney transplant is delayed may be rescreened for study eligibility. To reconfirm the participant's eligibility, all pre-study evaluations should be repeated, after approval from the Sponsor.

8.12.2 Treatment Period

Study intervention will begin within 7 days post-transplant and will continue through Week 28. The Day 1 Visit (as shown in the Study SoA, Section 1.3) will be the day the participant is allocated and study intervention is initiated (ie, Day 1).

Study visits in the treatment period will occur at Week 1, every two weeks from Week 2 through Week 12, and every 4 weeks from Week 16 through Week 28 (Section 1.3). At these scheduled visits, the investigator will perform an assessment of CMV disease, and participants' blood samples will be collected at scheduled timepoints (see Study SoA, Section 1.3) for CMV DNA PCR testing by the central laboratory in order to detect CMV DNAemia. The central laboratory CMV DNA PCR results will not be provided to the investigator but will be analyzed at the end of the study. Safety will also be evaluated while participants are on study intervention. Note that serum creatinine screening intervals should occur according to the local SOC (outside the context of the study) as part of a participant's SOC post-kidney transplantation.

8.12.2.1 Day 1 Visit

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

For WOCBP participants, a urine pregnancy test will be performed at the site prior to the initiation of study intervention. 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. A serum pregnancy test (within 72 hours before the first dose of study intervention) may be performed on Day 1 for those WOCBP participants who are anuric and/or unable to provide urine.

8.12.2.2 Study Intervention Administration

Within 7 days post transplant, following completion of the Day 1 procedures/assessments and confirmation of eligibility (including availability of results from samples for CrCl and liver function tests), the participant will be allocated. Sites should not allocate the participant for study intervention administration until the participant has met all eligibility criteria for the study and is ready to receive the first dose of LET on Day 1. The site pharmacist or study coordinator will select appropriate bottle(s) or vial(s) of study intervention to be administered.

The first dose of study intervention will be administered at the trial site with monitoring by investigative site personnel at the Day 1 Visit (note: after pre-dose PK sample collection on Day 1). Thereafter, at each scheduled visit during treatment period, participants will visit the trial site before taking the study intervention. The dose of study intervention will be administered appropriately at the trial site under the control of investigative site personnel.

For participants who cannot swallow and/or have 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. 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 (See Section 8.1.9).

After Day 1, study intervention will continue through Week 28, with the primary intent of preventing CMV disease/infection.

The participant will be instructed in the use of the Study Medication Diary to record the number of tablets of study intervention taken during the study treatment period. IV study intervention will be recorded by the site pharmacist or study personnel in the CRF.

8.12.3 Follow-up Period

After completion of study therapy at Week 28, participants will continue to be followed for efficacy and safety assessment, and complete all remaining visits through Week 52. Information will continue to be collected for (1) re-hospitalizations (including re-hospitalizations for CMV infection/disease), (2) all-cause mortality, (3) NODAT, (4) select OIs, (5) biopsy-proven acute renal graft rejections and graft loss, and (6) use of G-CSF.

During the follow-up period, samples for CMV DNA PCR should be sent to the central laboratory as per the Study SoA (Section 1.3).

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

Participants who discontinue study medication early (ie, prior to Week 28) due to any reason will complete all remaining treatment period visits through Week 28 as well as all remaining follow-up visits through Week 52 as outlined in the SoA (Section 1.3). All scheduled study

visits will be completed regardless of when cessation of study treatment occurs. All specified procedures will be completed for these participants during the treatment period (with the exception of study intervention administration, PK assessments, and study medication diary review) and in the follow-up period as outlined in the SoA (Section 1.3).

8.12.5 CMV Infection or Early Discontinuation Visit

8.12.5.1 CMV Infection Visit

The CMV Infection Visit will be performed if any of the following occurs: (1) any discontinuation of study treatment in response to suspected or confirmed CMV disease; (2) any discontinuation of study treatment and initiation of CMV treatment (excluding initiation of CMV prophylaxis following discontinuation of study treatment for non-CMV adverse events); or (3) initiation of CMV treatment during the follow-up period (see Section 1.3 [SoA]).

During study treatment period

If CMV disease is suspected or confirmed by the investigator or a clinical decision is made by the investigator to stop study treatment and start anti-CMV treatment based on positive results on locally performed CMV DNA PCR or CMV antigenemia 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 and a CMV viral resistance sample; see Section 1.3) will be completed prior to initiating anti-CMV treatment as an SOC for CMV disease/infection, which may be started at the investigator's discretion. These participants will complete all remaining treatment-period visits through Week 28 as well as all remaining visits through Week 52 as outlined in the Section 1.3 (SoA). All specified procedures through Week 28 will be completed for these participants with the exception of study intervention administration, PK assessments, 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 SOC treatment for CMV Disease/Infection for up to 7 days (inclusive) before the participant is permanently discontinued from study treatment (but remains in the study). If within the 7 day interval, CMV Disease/Infection 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 SOC treatment for CMV Disease and resume study treatment.

During follow-up period

If CMV disease is suspected or confirmed by the investigator or a clinical decision is made by the investigator to start anti-CMV treatment based on positive results on locally performed CMV DNA PCR or CMV antigenemia during the post-treatment follow-up period (ie, after completion or early discontinuation of study intervention): CMV Infection Visit (including collection of CMV DNA PCR and a CMV viral resistance sample; see Section

1.3) will be completed prior to initiating anti-CMV treatment as an SOC for CMV disease/infection, which may be started at the investigator's discretion. Participants may be started on SOC therapy for CMV disease/infection at the investigator's discretion and will complete all remaining follow-up visits (through Week 52). See Section 1.3 (SoA) for procedures performed at the CMV Infection Visit.

Note: It is mandatory to collect a confirmatory plasma sample for CMV DNA PCR testing at the central laboratory **immediately prior to** (ie, on the day of) initiating treatment for CMV disease/infection in **ALL** instances. In the event that the confirmatory result obtained on the day of initiation of anti-CMV treatment 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 treatment for CMV disease/infection (preferably within 48-72 hours; Section 8.2.1).

During the course of the study, a participant may undergo ≥1 CMV Infection Visit at the discretion of the investigator.

8.12.5.2 Early Discontinuation Visit

Early Discontinuation Visit will be performed when the participants discontinue study intervention or prematurely discontinue the study.

Study Intervention Discontinuation (During study treatment period)

Participants who discontinue study therapy prior to the last scheduled treatment visit for reasons other than CMV disease/infection should have an Early Discontinuation Visit and then complete all remaining treatment-period visits through Week 28, as well as all remaining visits through Week 52, as outlined in the SoA (Section 1.3). All specified procedures through Week 28 will be completed for these participants with the exception of study therapy administration, PK assessments, and study medication diary review. All scheduled study visits will be completed regardless of when cessation of study treatment occurs.

Early Study Discontinuation (During study treatment period or follow-up period)

The Early Discontinuation Visit will also be performed for all participants who prematurely discontinue the study prior to Week 52. It is very important to ensure that all procedures, as outlined in the Study SoA (Section 1.3), are performed in such participants at this visit prior to discontinuing the participant from the study. Most importantly, a plasma sample for CMV DNA PCR testing at the central laboratory should be collected at this visit.

During the course of the study, a participant may undergo Early Discontinuation Visit twice (ie, Study Intervention Discontinuation and Early Study Discontinuation).

9 STATISTICAL ANALYSIS PLAN

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

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan (SAP) 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 Safety, Efficacy and Pharmacokinetics of MK-8228 (Letermovir) for the Prevention of Human Cytomegalovirus (CMV) Infection and Disease in Adult Japanese Kidney Transplant Recipients
Treatment Assignment	All participants will be allocated to LET treatment group.
Analysis Populations	Efficacy: Full Analysis Set (FAS) population. Safety: All Participants as Treated (APaT) population
Primary Endpoint	• Adverse events (AEs) • Discontinuing study treatment due to AEs
Statistical Methods for Key Safety Analyses	The Safety analysis will be based on the APaT population. AEs will be summarized by the number and percentage of the subjects who experienced respective events. Change from baseline in laboratory tests, vital signs and ECG will be summarized by descriptive statistics.
Statistical Methods for Key Efficacy Analyses	The efficacy analysis will be based on the FAS population. The following proportion and 95% confidence interval (CI) will be provided by timepoint. · Adjudicated CMV disease or anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) · Adjudicated CMV disease · Quantifiable CMV DNAemia (central)

Interim Analyses	No interim analysis is planned in this trial.
Multiplicity	No multiplicity adjustment is planned in this trial.
Sample Size and Power	The planned sample size is 20 participants with at least 10 being D+/R−.

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 trial is being conducted as an open-label study, ie, subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. First database lock will be executed when all results of letermovir plasma concentrations become available for population PK and exposure-safety analyses to submit data to regulatory agencies. The results of population PK and exposure-safety analyses will be reported in a Modeling and Simulation report. Final database lock will be executed at the end of the study for safety and efficacy analyses. Additional database lock(s) may be conducted if needed.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Safety and efficacy endpoints that will be evaluated are listed below.

9.4.1 Safety Endpoints

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

9.4.2 Efficacy Endpoints

1. Adjudicated CMV disease or anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) through Week 28 and Week 52 post-transplant.

   Adjudicated CMV disease is defined as the presence of either CMV end-organ disease or CMV syndrome and will be confirmed by an independent CAC. Only CAC-confirmed ("adjudicated") cases will be included in number of participants who met the endpoint. Investigator-assessed cases which are not confirmed by the CAC will not be included. Concordance/discordance between CAC and investigator assessment will be summarized.

Anti-CMV treatment based on 1) positive results on CMV antigenemia (local) or 2) quantifiable CMV DNAemia (local) is defined as initiation of approved anti-CMV agents (GCV, VGCV and/or foscarnet) based on at least one positive cell on CMV antigenemia and/or numeric value (not including the result of "Detected but not quantifiable") of CMV DNA PCR assay performed locally. CMV DNA test and/or CMV antigenemia results obtained from an investigator site-specific laboratory will be used to determine CMV infection.

2. Adjudicated CMV disease through Week 28 and Week 52 post-transplant.

3. Quantifiable CMV DNAemia (central) through Week 28 and Week 52 post-transplant.

   Quantifiable CMV DNAemia (central) is defined as any case with a numeric value or >910,000,000 (not including reporting of PCR results as "detected, not quantifiable") using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) assay, which will be performed by the central laboratory. CMV DNA test results obtained from an investigator site-specific laboratory will not be used to determine quantifiable CMV DNAemia (central). Quantifiable CMV DNAemia may be considered as a subset of CMV infection, which is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen.

9.4.3 Exploratory endpoints

1. Allograft dysfunction and/or rejection through 28 weeks post-transplant and 52 weeks post-transplant

   a. A ≥20% decline in post-transplant eGFR (using Modification of Diet in Renal Disease [MDRD] formula) from 4 weeks post-transplant (baseline) through 28 weeks post-transplant and 52 weeks post-transplant

   b. A biopsy-proven acute renal graft rejection through 28 weeks post-transplant and 52 weeks post-transplant

   c. Graft loss through 28 weeks post-transplant and 52 weeks post-transplant

2. NODAT through 28 weeks post-transplant and 52 weeks post-transplant

   Of the participants identified by the investigator as developing NODAT during the study, the study team will perform a confirmatory analysis of NODAT.

3. Selected health outcomes (in addition to NODAT, see above) as follows:

   a. All-cause mortality through 28 weeks post-transplant and 52 weeks post-transplant

b. All re-hospitalizations (following initial hospital discharge) and re-hospitalizations for CMV infection/disease through 28 weeks post-transplant and 52 weeks post-transplant

c. Select OIs through 28 weeks post-transplant and 52 weeks post-transplant

d. More than one use of any G-CSF within any consecutive 30-day period beginning on Day 1 of treatment through the end of the treatment period.

4. Antiviral resistance to LET in prophylaxis failures through 52 weeks post-transplant

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

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all subjects 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 each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.2 Efficacy Analysis Populations

The FAS population will serve as the population for the analysis of efficacy data in this study. The FAS population consists of all subjects who:

- received at least one dose of study treatment
- D+/R−, D+/R+ or D−/R+
- No detectable CMV DNA (measured by central laboratory) on Day 1

9.6 Statistical Methods

9.6.1 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 through the end of the treatment period. Drug-related SAEs which are collected throughout the study will also be assessed through Week 52.

AEs, study drug discontinuation due to AEs and other safety events will be summarized using the number and percentage of the subjects who experienced respective events. Change from baseline in laboratory tests, vital signs and ECG at respective timepoints will be summarized using descriptive statistics. Baseline is defined as the last available measurement prior to enrollment.

9.6.2 Statistical Methods for Efficacy Analyses

For all binary efficacy endpoints, the proportion and corresponding 95% CI will be provided by timepoint. The calculation is based on the exact binomial method proposed by Clopper and Pearson (1934). Continuous efficacy measurement will be summarized descriptively. The results will be provided by all participants, D+/R− and R+. Methods related to exploratory objectives will be described in the sSAP.

9.6.2.1 Missing Data Handling

There are two types of missing values:

- Intermittent missing values due to a missed or skipped visit. This applies only to those endpoints evaluated prior to 52 weeks post-transplant. Participants who had missing information at the end of the trial are monotone missing.
- Monotone (non-intermittent) missing due to premature discontinuation from the study for any reason.

Table 6 provides an approach to handle of missing values.

Table 6 Approach to Handle Missing Values

Approach	Intermittent Missing	Monotone Missing
Observed Failure	Excluded	No failure
NC = F	Failure	Failure
F = Failure; NC = Non Completer		

The primary missing data approach will be Observed Failure (OF) approach. NC = F approach will be used for supportive analyses.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

The number and percentage of participants screened and allocated, and the primary reasons for screening failure, and discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

9.6.3.2 Pharmacokinetic Analyses

The PK data obtained from this study will be used to characterize the PK of LET in Japanese kidney transplant recipients. Intensive PK data will be analyzed by non-compartment

analysis. Descriptive statistics (number of participants, arithmetic mean, standard deviation, coefficient of variance, geometric mean, geometric coefficient of variance, minimum, median and maximum) of PK parameters (see Section 4.2.1.3) will be provided. Population PK analysis will be conducted, if needed. The prospective details of this population PK analysis will be specified in a separate Modeling and Simulation analysis plan.

9.7 Interim Analyses

No interim analysis is planned for the study.

9.8 Multiplicity

No adjustment for multiplicity is planned for the study.

9.9 Sample Size and Power Calculations

A total of 20 participants will be enrolled in the treatment period. The sample size was derived based on feasibility of enrollment, in consideration of the limited number of D+/R− and R+ kidney transplants conducted in Japan.

If a specific AE is not observed in any of the 20 participants, then the true incidence of that event is 11% or less with 90% confidence.

9.10 Subgroup Analyses

The consistency of the treatment effect will be assessed descriptively via summary statistics by CMV seropositivity subgroups D+/R− and R+.

9.11 Compliance (Medication Adherence)

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 allocation to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study medication, the “Number of Days Should be on Therapy” is the total number of days from allocation to the date of the last dose of study medication. Percent compliance for each participant will be calculated using the following formula:

(Number of Days on Therapy / Number of Days Should be on Therapy) x 100.

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

9.12 Extent of Exposure

The extent of exposure of study treatment will be evaluated by summary statistics 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 Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Clinical Adjudication Committee (CAC)

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

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 International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and 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, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 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 Studies.

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory unless otherwise specified within the protocol.

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

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

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

- Pregnancy testing

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the subject's participation in the study.

  - A serum pregnancy test may be performed for those WOCBP participants who are anuric and/or unable to provide urine.

Table 7 Protocol-required Laboratory Assessments

Hematology[a]	Chemistry[a]	Urinalysis[a]	Other
RBC count	Albumin	Blood	HBsAg[b]
Hematocrit	Alkaline phosphatase	Glucose	HCV-Ab[b]
Hemoglobin	ALT	Protein	Hepatitis C RNA PCR[b]
Platelet count	AST	Specific gravity	HIV antibody[b]
WBC count with differential:	Bicarbonate	Microscopic examination, if abnormal results are noted	CMV IgG Antibody
Neutrophils	Calcium		
Lymphocytes	Chloride		CMV DNA PCR[c]
Monocytes	Creatinine		QuantiFERON-CMV Assay
Eosinophils	Glucose		CMV viral resistance testing[d]
Basophils	Phosphorus		
	Potassium		Coagulation: PT/INR[a]
	Sodium		
	Total Bilirubin		Urine hCG[e]
	Direct Bilirubin		Serum β hCG[e]
	Indirect Bilirubin		
	Total protein		
	Blood Urea Nitrogen		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; hCG = human chorionic gonadotropin; CMV = cytomegalovirus; HBsAg = Hepatitis B surface antigen; HCV-Ab = Hepatitis C virus antibody; HIV = human immunodeficiency virus; IgG = immunoglobulin G; INR = International normalized ratio; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SOC = standard of care; WBC = white blood cell

a. For screening, values from the participant's chart within 14 days prior to screening for required chemistry, hematology, coagulation, and urinalysis tests are acceptable. If not available, this testing may be performed by the central laboratory or locally per SOC.
b. Hepatitis B, C testing only performed if results not previously documented within 90 days of Day 1. If HCV-Ab is positive, HCV RNA PCR results should be provided (or, if not available, HCV RNA PCR testing will be performed by the central or local laboratory). HIV antibody test results documented at any time prior to allocation of the participant will be acceptable; a copy of this HIV report must be available. If documentation of a previous HIV test is not available, the HIV antibody test must be conducted using the central or local laboratory.
c. Protocol-specified CMV DNA PCR testing will be performed by the central laboratory using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) System.
d. CMV viral resistance testing to be performed only for participants if any of the following occurs: (1) any discontinuation of study treatment in response to suspected or confirmed CMV disease; (2) any discontinuation of study treatment and initiation of anti-CMV treatment; or (3) initiation of anti-CMV treatment during the follow-up period.
e. May use local or central laboratory serum pregnancy test if unable to provide urine.

The investigator must document their review of each laboratory safety report.

The central laboratory based CMV DNA PCR and QuantiFERON-CMV assay results will not be shared with the respective site investigators.

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

10.3.1 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.

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

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

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

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

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

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

number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity

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

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

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

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

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

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary,

etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 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 nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Female Participants

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.*
• Intrauterine hormone-releasing system (IUS)[c,d] • Intrauterine device (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 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 contraception - Oral
• Progestogen-only hormonal contraception - Oral
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.
Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[e]
[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] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation [d] IUS is a progestin releasing IUD. [e] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@msd.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Definition of CMV Disease

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. • Detection of fungal copathogens like *Aspergillus spp.* + "halo" sign (radiology) indicates fungal, rather than CMV pneumonia.[a] • 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.

CMV Disease Type	Probable	Proven	Notes
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.
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.

CMV Disease Type	Probable	Proven	Notes
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
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

CMV Disease Type	Probable	Proven	Notes
CMV syndrome	Two or more of the following: 1) Fever ≥38°C for at least 2 days 2) New or increased malaise or new or increased fatigue[b] 3) Leukopenia or neutropenia on two separate measurements at least 24 hours apart[c] 4) ≥5% atypical lymphocytes 5) Thrombocytopenia[d] 6) Elevation of ALT or AST to 2 × ULN **AND** Evidence of CMV in blood by viral isolation, rapid culture, antigenemia, or nucleic acid testing	N/A	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; PCR = polymerase chain reaction; ULN = upper limit of normal.

a. The presence of co-pathogens, such as Aspergillus species together with typical radiologic signs of Aspergillus pneumonia, would indicate fungal pneumonia, although a role of CMV cannot be conclusively excluded if the criteria for CMV disease are otherwise met. It is therefore recommended that studies report separately cases where CMV disease is found with or without co-pathogens with details given on the co-pathogens [Ljungman, P., et al 2016].

b. New or increased malaise (Toxicity Grade 2): uneasiness or lack of well-being; limiting instrumental Activities of Daily Living. New or increased fatigue (Toxicity Grade 3): fatigue not relieved by rest, limiting self-care Activities of Daily Living Toxicity grade according to National Cancer Institute: Common Terminology Criteria for Adverse Events, Version 4.0

c. Leukopenia or neutropenia on 2 separate measurements at least 24 hours apart, defined as a white blood cell (WBC) count of <3500 cells/µL, if the WBC count prior to the development of clinical symptoms was ≥4000 cells/µL, or a WBC decrease of >20%, if the WBC count prior to the development of clinical symptoms was <4000 cells/µL. The corresponding neutrophil counts are <1500 cells/µL or a decrease of >20% if the neutrophil count before the onset of symptoms was <1500 cells/µL [Ljungman, P., et al 2016].

d. Thrombocytopenia defined as a platelet count of <100 000 cells/µL if the platelet count prior to the development of clinical symptoms was ≥115 000 cells/µL or a decrease of >20% if the platelet count prior to the development of clinical symptoms was <115 000 cells/µL [Ljungman, P., et al 2016].

[Ljungman, P., et al 2016] [National Cancer Institute 2009]

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	>3.5 g/dL	2.8 – 3.5 g/dL	<2.8 g/dL
INR[b]	<1.7	1.7 – 2.3	>2.3

INR = international normalized ratio

[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.

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: Blood Volume Table

Study Period	Pre-Treatment	Treatment												Follow-up						CMV Infection and/or Early Discon Visit
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Visit Name	SCR	D1	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	
Blood Parameter	Approximate Blood Volume (mL)																			
Hematology[a]	2	2	2		2		2		2	2	2	2	2	2						2
Chemistry[a]	7	7	7		7		7		7	7	7	7	7	7						7
Coagulation[a]	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8						1.8
Serum pregnancy Test (WOCBP only, if unable to provide urine)	2	2			2		2		2	2	2	2	2	2						2
HIV and Hepatitis B and C Screen[b]	11																			
Blood for Genetic Analysis	8.5																			
CMV DNA PCR[c]		3		3	3		3		3	3	3	3	3	3	3	3	3	3	3	3
QuantiFERON-CMV Assay	3								3				3			3			3	3
CMV Viral Resistance Testing[d]																			5	5[e]
Trough PK and Week 1 Intensive PK		3	18	3	3	3	3	3	3	3	3	3	3							3
Additional Intensive PK for participants with dose formulation switch			←----------18 (performed at most once during the study; this volume is NOT included in the Expected Total volume)----------→																	

Study Period	Pre-Treatment	Treatment												Follow-up						CMV Infection and/or Early Discon Visit
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Visit Name	SCR	D1	W1	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	
Expected Total (mL)	35.3	18.8	28.8	7.8	18.8	4.8	18.8	4.8	21.8	18.8	18.8	18.8	21.8	15.8	3	6	3	3	11	31.8

CMV = cytomegalovirus; D = Day; DNA = deoxyribonucleic acid; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; PK = pharmacokinetic; RNA = ribonucleic acid; SCR = screening; SOC = standard of care; W = Week

a. For screening, values from the participant's chart within 14 days prior to screening for required chemistry, hematology, and coagulation tests are acceptable. If not available, this testing may be performed by the central laboratory or locally per SOC.
b. Hepatitis B, C testing only performed if results not previously documented within 90 days of Day 1. If hepatitis C virus antibody is positive, HCV RNA PCR results should be provided (or, if not available, HCV RNA PCR testing will be performed by the central or local laboratory). HIV antibody test results documented at any time prior to allocation of the participant will be acceptable; a copy of this HIV report must be available. If documentation of a previous HIV test is not available, the HIV antibody test must be conducted using the central or local laboratory.
c. Protocol-specified CMV DNA testing will be performed by the central laboratory using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) System.
d. To be performed only for participants who discontinue study treatment due to CMV disease or in whom anti-CMV treatment is started.
e. A repeat sample should be collected at the next scheduled visit after the CMV Infection Visit.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
APaT	All Participants as Treated
AST	Aspartate aminotransferase
AUC_{tau}	Area under the concentration-time curve to the end of the dosing period
β-hCG	β-human chorionic gonadotropin
BAL	Bronchoalveolar lavage
BCRP	Breast cancer resistance protein
BID	Twice daily
CAC	Clinical Adjudication Committee
C_{eoi}	Concentration at the end of infusion
CI	Confidence interval
CL_{ss}	Clearance at steady state
CL_{ss}/F	Apparent clearance at steady state
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CrCl	Creatinine clearance
CRF	Case Report Form
CsA	Cyclosporin A
CSR	Clinical Study Report
CSF	Cerebrospinal fluid
CTFG	Clinical Trial Facilitation Group
C_{trough}	Trough concentration
CYP	Cytochrome P450
D	Doner
DB	Dense body
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DNAemia	Detection of DNA in samples of plasma, whole blood, and isolated peripheral blood leukocytes or in buffy-coat specimens
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
EDC	Electronic data collection
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GCV	Ganciclovir
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody

Abbreviation	Expanded Term
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HMG-CoA reductase	Hydroxymethylglutaryl-CoA reductase
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
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
KDIGO	Kidney Disease Improves Global Outcomes
LET	Letermovir
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
MDRD	Modification of Diet in Renal Disease
NC = F	Non Completer = Failure
NIMP	Non-Investigational Medicinal Product
NODAT	New onset diabetes mellitus after transplant
NTR	Narrow therapeutic range
OATP	Organic anion-transporting polypeptide
OF	Observed Failure
OI	Opportunistic infection
PCR	Polymerase chain reaction
PET	Pre-emptive therapy
PK	Pharmacokinetic
PO	Orally
PT	Prothrombin time
QD	Once daily
R	Recipient
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCR	Screening
SMD	Study medication diary
SoA	Schedule of activities
SOC	Standard of care
SOT	Solid organ transplant
SUSAR	Suspected unexpected serious adverse reaction
T_{max}	Time to reach maximum concentration
Tp	Transplant
ULN	Upper limit of normal
VGCV	Valganciclovir
VZV	Varicella zoster virus

Abbreviation	Expanded Term
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman/women of childbearing potential

11 REFERENCES

[Abate, D., et al 2013] Abate D, Saldan A, Mengoli C, et al. Comparison of cytomegalovirus (CMV) enzyme-linked immunosorbent spot and CMV quantiferon gamma interferon-releasing assays in assessing risk of CMV infection in kidney transplant recipients. J Clin Microbiol. 2013;51:2501-7.

[Bayer, N. D., et al 2010] Bayer ND, Cochetti PT, Anil Kumar MS, et al. Association of metabolic syndrome with development of new-onset diabetes after transplantation. Transplantation. 2010;90:861-6.

[Beam, E. et al 2012] Beam E, Razonable RR. Cytomegalovirus in solid organ transplantation: epidemiology, prevention, and treatment. Curr Infect Dis Rep. 2012;14:633-41.

[Becke, S., et al 2010] Becke S, Aue S, Thomas D, et al. Optimized recombinant dense bodies of human cytomegalovirus efficiently prime virus specific lymphocytes and neutralizing antibodies without the addition of adjuvant. Vaccine. 2010;28:6191-8.

[Boeckh, M. 2011] Boeckh M. Complications, diagnosis, management, and prevention of CMV infections: Current and future. Hematology Am Soc Hematol Educ Program. 2011;2011:305-9.

[Boivin, G., et al 2012] Boivin G, Goyette N, Farhan M, et al. Incidence of cytomegalovirus UL97 and UL54 amino acid substitutions detected after 100 or 200 days of valganciclovir prophylaxis. J Clin Virol. 2012 ;53:208-13.

[Cantisan, S., et al 2013] Cantisan S, Lara R, Montejo M, et al. Pretransplant interferon-γ secretion by CMV-specific CD8+ T cells informs the risk of CMV replication after transplantation. Am J Transplant. 2013;13:738-45.

[Doyle, A. M., et al 2006] Doyle AM, Warburton KM, Goral S, et al. 24-week oral ganciclovir prophylaxis in kidney recipients is associated with reduced symptomatic cytomegalovirus disease compared to a 12-week course. Transplantation. 2006;81:1106-11.

[Fernandez-Ruiz, M., et al 2014] Fernandez-Ruiz M, Kumar D, Humar A. Clinical immune-monitoring strategies for predicting infection risk in solid organ transplantation. Clin Transl Immunology. 2014;3:e12.

[Goldner, T., et al 2011] Goldner T, Hewlett G, Ettischer N, et al. The novel anticytomegalovirus compound AIC246 (letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase. J Virol. 2011;85:10884-93.

[Hartmann, A., et al 2006] Hartmann A, Sagedal S, Hjelmesaeth J. The natural course of cytomegalovirus infection and disease in renal transplant recipients. Transplantation. 2006;82(2 Suppl):S15-7.

[Hjelmesaeth, J., et al 2005] Hjelmesaeth J, Muller F, Jenssen T, et al. Is there a link between cytomegalovirus infection and new-onset posttransplantation diabetes mellitus? Potential mechanisms of virus induced beta-cell damage. Nephrol Dial Transplant. 2005;20:2311-5.

[Hodson, E. M., et al 2013] Hodson EM, Ladhani M, Webster AC, et al. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev. 2013;(2):CD003774.

[Humar, A., et al 2010] Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. Am J Transplant. 2010;10:1228-37.

[Husain, S., et al 2009] Husain S, Pietrangeli CE, Zeevi A. Delayed onset CMV disease in solid organ transplant recipients. Transpl Immunol. 2009;21:1-9.

[Japan Prescribing Information, PREVYMIS 2018] Japan Prescribing Information: PREVYMIS tablets, PREVYMIS intravenous infusion: Mar 2018.

[Japan Prescribing Information, VALIXA 2018] Japan Prescribing Information: VALIXA tablets and dry syrup: Aug 2018.

[Japanese Society for Clinical Renal Transplantation, 2018] Japanese Society for Clinical Renal Transplantation and The Japan Society for Transplantation. Annual Progress Report from the Japanese Renal Transplant Registry: Number of Renal Transplantations in 2017 and a Follow-up Survey. 2018 [Japanese]

[Japanese Society for Clinical Renal Transplantation Guideline Work Group 2011; Addendum in 2015] Japanese Society for Clinical Renal Transplantation Guideline Work Group. Clinical Practice Guideline on the Management of Cytomegalovirus Disease in Renal Transplantation 2011; Addendum in 2015 [Japanese]

[Kalil, A. C., et al 2005] Kalil AC, Levitsky J, Lyden E, et al. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med. 2005;143:870-80.

[Kaul, D. R., et al 2011] Kaul DR, Stoelben S, Cober E, et al. First report of successful treatment of multidrug-resistant cytomegalovirus disease with the novel anti-CMV compound AIC246. Am J Transplant. 2011;11:1079-84.

[Kidney Disease: Improving Global Outcomes Transplant Work Group 2009] Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9 Suppl 3:S1-155.

[Kotton, C.N., et al, 2018] Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018;102:900-31.

[Kranz, B., et al 2008] Kranz B, Vester U, Wingen AM, et al. Acute rejection episodes in pediatric renal transplant recipients with cytomegalovirus infection. Pediatr Transplant. 2008;12:474-8.

[Kropeit, D., et al 2017] Kropeit D, Scheuenpflug J, Erb-Zohar K, et al. Pharmacokinetics and safety of letermovir, a novel anti-human cytomegalovirus drug, in patients with renal impairment. Br J Clin Pharmacol. 2017;83:1944-53.

[Lischka, P., et al 2010] Lischka P, Hewlett G, Wunberg T, et al. In vitro and in vivo activities of the novel anticytomegalovirus compound AIC246. Antimicrob Agents Chemother. 2010;54:1290-7

[Ljungman, P., et al 2016] Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials. Clin Infect Dis. 2016.

[Lowance, D., et al 1999] Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. N Engl J Med. 1999;340:1462-70.

[Lurain, N. S. and Chou, S. 2010] Lurain NS, Chou S. Antiviral drug resistance of human cytomegalovirus. Clin Microbiol Rev. 2010;23:689-712.

[Manuel, O., et al 2013] Manuel O, Husain S, Kumar D, et al. Assessment of cytomegalovirus-specific cell-mediated immunity for the prediction of cytomegalovirus disease in high-risk solid-organ transplant recipients: a multicenter cohort study. Clin Infect Dis. 2013;56:817-24.

[Martin, S. I., et al 2013] Martin SI, Fishman JA; AST Infectious Diseases Community of Practice. Pneumocystis pneumonia in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:272-9.

[Marty, F. M., et al 2017] Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017;377:2433-44.

[National Cancer Institute 2009] National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 4.0. U.S.Department of Health and Human Services; 2009. 79p.

[Razonable, R. R. 2013] Razonable RR. Management strategies for cytomegalovirus infection and disease in solid organ transplant recipients. Infect Dis Clin North Am. 2013;27:317-42.

[Rubin, R. H. 2007] Rubin RH. The pathogenesis and clinical management of cytomegalovirus infection in the organ transplant recipient: the end of the 'silo hypothesis'. Curr Opin Infect Dis. 2007;20:399-407.

[Schnitzler, M. A., et al 2003] Schnitzler MA, Lowell JA, Hardinger KL, et al. The association of cytomegalovirus sero-pairing with outcomes and costs following cadaveric renal transplantation prior to the introduction of oral ganciclovir CMV prophylaxis. Am J Transplant. 2003;3:445-51.

[Trofe-Clark, J. and Sawinski, D. 2016] Trofe-Clark J, Sawinski D. BK and other polyomaviruses in kidney transplantation. Semin Nephrol. 2016;36:372-85.

[Valentine, V. G., et al 2008] Valentine VG, Weill D, Gupta MR, et al. Ganciclovir for cytomegalovirus: a call for indefinite prophylaxis in lung transplantation. J Heart Lung Transplant. 2008;27:875-81.