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Title Page

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Protocol Title: A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients

Protocol Number: 002-05

Compound Number: MK-8228

Sponsor Name and Legal Registered Address:

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

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND NUMBER: 104,706 (tablet IND); 118,361 (IV IND)

EudraCT NUMBER: 2017-001055-30

Approval Date: 27-August-2019

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

I agree to conduct this clinical trial 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
P002-05	27-Aug-2019	To add the requirement that the intravenous (IV) formulation of letermovir (LET) supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials. This requirement is being added to prevent the possible administration of product-related particulate matter. The presence of visible product-related particulate matter is an expected characteristic of new clinical supplies of the IV formulation of LET. This requirement is being implemented to allow for the release of new clinical supplies of IV LET, and as a precaution, it must be applied regardless of whether the clinical site considers its current clinical supply to be impacted. In addition, where applicable, the matching placebo to the IV formulation of acyclovir must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter and using DEHP-free IV bags and infusion set materials, in order to maintain the blind for IV study medications.
P002-04	11-Feb-2019	To add strong and moderate inducers of transporters (eg, P-glycoprotein [P-gp]) and/or enzymes (eg, uridine diphosphate glucuronosyltransferase [UGT]) to the list of prohibited medications due to the potential for co-administration to result in a decrease in letermovir plasma concentrations.
P002-03	29-May-2018	To permit potential participants to be consented and screened up to 5 days (inclusive) after transplant surgery instead of requiring the completion of all screening procedures prior to transplant. Extending the screening to the post-transplant period will facilitate the screening and enrollment of deceased donor transplant recipients who are typically under time constraints immediately prior to the transplant surgery and also will provide additional time for the investigator to obtain the required screening laboratory results after the transplant surgery.

Document	Date of Issue	Overall Rationale
P002-02	21-Feb-2018	To add two laboratory exclusion criteria for consistency with the valganciclovir (VGCV) product circular information.
P002-01	07-Dec-2017	To add a letermovir (LET) 240 mg dose group when administered intravenously (IV) without cyclosporine (CsA). LET has previously been evaluated in a Phase 3 trial in hematopoietic stem cell transplant (HSCT) recipients at doses of 240 mg PO or IV when administered with CsA, and 480 mg PO or IV when administered without CsA. All doses were generally well-tolerated and efficacious; however, LET exposures (steady state median AUC) in HSCT recipients with the 480 mg IV dose (without CsA) were higher than in the other three dose groups. Population pharmacokinetic (PK) simulations using data from the Phase 3 trial in HSCT recipients suggest that a 240 mg IV dose (without CsA) will provide exposures comparable to exposures obtained following administration of a 480 mg PO dose (without CsA). Therefore, an additional dose group of 240 mg IV (without CsA) is being added to the current protocol to evaluate the PK, efficacy, and safety of this dose in transplant recipients. Participants who receive IV LET (without CsA) will be randomized 1:1 to receive either a 480 mg or 240 mg dose.
P002-00	21-Sep-2017	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 05

Overall Rationale for the Amendment:

To add the requirement that the intravenous (IV) formulation of letermovir (LET) supplied by the Sponsor to sites as study medication must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials. This requirement is being added to prevent the possible administration of product-related particulate matter. The presence of visible product-related particulate matter is an expected characteristic of new clinical supplies of the IV formulation of LET. This requirement is being implemented to allow for the release of new clinical supplies of IV LET, and as a precaution, it must be applied regardless of whether the clinical site considers its current clinical supply to be impacted. In addition, where applicable, the matching placebo to the IV formulation of acyclovir must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter and using DEHP-free IV bags and infusion set materials, in order to maintain the blind for IV study medications.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
7.4, Blinding 7.5.1, Dose Preparation 9.1.9, Treatment Administration	Added information regarding the requirement that the IV formulation of letermovir (LET) and, where applicable, matching placebo to IV acyclovir, must be administered through a sterile 0.2-micron or 0.22-micron polyethersulfone (PES) in-line filter and using diethylhexyl phthalate (DEHP)-free IV bags and infusion set materials.	To align with the overall rationale for the amendment as detailed in the beginning of the document.
7.1, Treatments Administered	Removed option for IV acyclovir or matching placebo to IV acyclovir to be prepared with	To maintain the blind for IV study medications.

Section # and Name	Description of Change	Brief Rationale
7.4, Blinding 7.5.1, Dose Preparation	125-mL bags and clarified that IV acyclovir or matching placebo to IV acyclovir must be prepared with 250-mL bags.	
2, Schedule of Activities 9.5.3, Vital Signs	Removed note/text requiring vital signs to be measured in a semi-recumbent position and following resting in a semi-recumbent position.	Removal of unnecessary operational restraint.
6.2, Exclusion Criteria	Added “for the purposes of this protocol, dialysis includes hemofiltration” to Note in Exclusion Criterion 5.	Acknowledgment that dialysis, for the purposes of this protocol, includes hemofiltration.
6.2, Exclusion Criteria 7.6, Treatment Compliance 9.1.6, Kidney Transplant/Dialysis Details Review 9.1.9.1, Timing of Dose Administration 10.6.3.1, Demographic and Baseline Characteristics	Added “plasmapheresis” to text.	Since there are insufficient data in patients on plasmapheresis to make letermovir dosing recommendations, all applicable aspects of the protocol involving hemodialysis, eg, exclusion criteria, study medication dosing recommendations, and data collection, will also apply to plasmapheresis.

Section # and Name	Description of Change	Brief Rationale
7.7, Concomitant Therapy	Broadened prohibition of imipenem-cilastatin beyond coadministration with VGCV/GCV.	Clarification that imipenem-cilastatin is a prohibited concomitant medication.
9.5.8.2, CMV DNA PCR Testing	Removed text "…based on clinical suspicion of CMV disease…".	Clarification to permit sites to locally monitor CMV DNA levels whenever clinically indicated, regardless of whether CMV disease is suspected.
9.11.4.1, ~~Discontinuation Due to~~ CMV Disease Visit	Changed title of section from "Discontinuation Due to CMV Disease" to "CMV Disease Visit" Added text to clarify that one of the CMV Disease Visit criteria (any discontinuation of study treatment and initiation of CMV treatment) excludes initiation of CMV prophylaxis following discontinuation of study treatment for non-CMV adverse events.	To harmonize the title of the section with its contents describing the criteria and procedures for the CMV Disease Visit. To provide investigators and sites with additional clarification on protocol-specified criteria for performing a CMV Disease Visit, since the initiation of CMV prophylaxis following discontinuation of study treatment for non-CMV adverse events is not consistent with clinical management of confirmed or suspected CMV disease.
10.6.1.3 Missing Data Handling	Removed treatment related discontinuation = failure (TRD=F) sensitivity analysis from text and from Table 13	To align with subject disposition eCRF available choices for end of study. This analysis cannot be performed because the choice of discontinuation from study due to adverse event is no longer available.

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1. Synopsis

Protocol Title:

A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients

Short Title:

LET vs VGCV for Prevention of CMV disease in Kidney Transplant Recipients

Objectives/Hypotheses and Endpoints:

In adult D+/R- (ie, CMV seropositive organ donor/CMV seronegative organ recipient) kidney transplant recipients:

Objective/Hypothesis	Endpoint
Primary	

• Objective: To evaluate the efficacy of letermovir (LET) versus valganciclovir (VGCV), as measured by the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant.
  • Hypothesis (H1): LET is non-inferior to VGCV in the prevention of CMV disease through 52 weeks post-transplant.
  • Hypothesis (H2): LET is superior to VGCV in the prevention of CMV disease through 52 weeks post-transplant. Hypothesis testing will be performed only if non-inferiority is demonstrated.
	• CMV disease

Secondary	
• Objective: To evaluate the efficacy of LET versus VGCV, as measured by the proportion of participants with adjudicated CMV disease through 28 weeks post-transplant.	• CMV disease

• Objective: To evaluate the efficacy of LET versus VGCV, as measured by the time to onset of adjudicated CMV disease through 52 weeks post-transplant.	• Time to onset of adjudicated CMV disease through 52 weeks post-transplant
• Objective: To evaluate the safety and tolerability of LET versus VGCV.	• Accumulated safety data (adverse events, laboratory, vital signs, etc.)

Overall Design:

Study Phase	Phase 3
Clinical Indication	Prevention of CMV disease in D+/R- kidney transplant recipients
Population	Adult D+/R- kidney transplant recipients
Study Type	Interventional
Type of Design	Active comparator, multi-site, randomized
Type of Control	Active control (VGCV)
Study Blinding	Double-blind
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 40 months from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 600 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	ARM 1: LET administration as follows: i. Oral administration of LET 480 mg once daily (QD), or ii. Oral administration of LET 240 mg QD if given concomitantly with cyclosporin A (CsA), or iii. IV administration of LET 480 mg QD, or iv. IV administration of LET 240 mg QD, or v. IV administration of LET 240 mg QD if given concomitantly with CsA

	with VGCV matching placebo (for oral administration), and acyclovir (ACV) 400 mg orally or 250 mg/m^2 intravenously starting within 7 days post-transplant and continuing through Week 28; the dose of ACV will be modified based on creatinine clearance. Note: For IV administration of LET, participants on concomitant CsA will receive 240 mg IV LET QD, while participants not on concomitant CsA will be randomized 1:1 to receive either 240 mg IV LET QD or 480 mg IV LET QD. ARM 2: Oral VGCV 900 mg QD or intravenous administration of ganciclovir (GCV) 5 mg/kg QD with LET matching placebo (for oral administration), and ACV matching placebo (for both oral and intravenous [IV] administration) starting within 7 days post-transplant and continuing through Week 28; the dose of VGCV and GCV will be modified based on creatinine clearance.
Duration of Participation	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 signs the Informed Consent Form (ICF) through the final contact. The screening duration will be approximately 6 days for participants who receive a kidney from a deceased donor or up to 19 days for participants who receive a kidney from a living donor. Participants will then be randomized within 7 days post-transplant and receive assigned treatment through approximately Week 28. After the end of treatment, each participant will be followed through approximately Week 52.

A list of abbreviations used in this document can be found in Appendix 1. Study governance considerations are outlined in Appendix 3.

2. Schedule of Activities (SoA)

Study Period	Pre-Treatment		Treatment												Follow-Up						CMV Disease and/or Early Discon Visit	Notes
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[a]**	**Day of Tp**	**D1[b]**	**W 1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**		• 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". See Footnote a for screening window.
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for FBR	X																					
Intensive PK Consent	X																					For participants of non-Asian descent eligible for optional intensive PK
Participant Identification Card	X																					
Inclusion/Exclusion Criteria	X		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	
Treatment Allocation/ Randomization			X																			

Study Period	Pre-Treatment		Treatment												Follow-Up						CMV Disease and/or Early Discon Visit	Notes
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[a]**	**Day of Tp**	**D1[b]**	**W 1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**		• 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". See Footnote a for screening window.
Administration/ Dispensing: LET+Placebo to VGCV+ACV **or** VGCV+Placebo to LET+Placebo to ACV			X		X	X	X	X	X	X	X	X	X									IV formulation (ie, IV LET, IV GCV, and IV ACV) available for participants unable to tolerate swallowing and/or have a condition that may interfere with the absorption of oral formulation. Contact IVRS/IWRS at all dispensing visits for assignment of study therapy (see Section 9.11.2.2).
Kidney Transplant/Dialysis Details Review			X																			
Study Medication Reconciliation and Diary Review			X	X	X	X	X	X	X	X	X	X	X	X							X	Participant will be trained in the use of Study Medication Diary on Day 1.
Efficacy Procedures																						
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
Safety Procedures																						
Full Physical Examination	X		X											X								
Height	X																					
Weight	X													X							X	

Study Period	Pre-Treatment		Treatment												Follow-Up						CMV Disease and/or Early Discon Visit	Notes
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[a]	Day of Tp	D1[b]	W 1	W 2	W 4	W 6	W 8	W 10	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52		• 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". See Footnote a for screening window.
Targeted 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 (heart rate, blood pressure, respiratory rate, body temperature)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead Electrocardiogram	X				X									X								Read locally. Screening values collected within 3 months prior to screening may be used. Semi-recumbent position.
Child-Pugh Score	X		X	X	X	X	X	X	X	X	X	X	X	X								See Appendix 8.
Participant Confirmation of Birth Control	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	
Adverse Events Monitoring	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 9.5.7 (including infusion site reactions).
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. If not available, testing may be performed by the central laboratory or locally as per SOC.
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 Disease and/or Early Discon Visit	Notes
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[a]**	**Day of Tp**	**D1[b]**	**W 1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**		• 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". See Footnote a for screening window.
Pregnancy Test (WOCBP only)	X																					Per pre-op SOC at the site (either urine or serum pregnancy test)
Urine Pregnancy Test (WOCBP only)			X			X		X		X	X	X	X	X	X	X	X				X	Performed locally; may use serum pregnancy test (local or central laboratory) if unable to provide urine
Serum Inhibin B, LH, FSH, Testosterone Levels in Men			X											X						X	X	Performed by the central laboratory
HIV and Hepatitis B and C Screen	X																					See Section 9.11.1, Screening for details on testing.
CMV Procedures/Assessments																						
CMV DNA PCR[c]			X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	Performed by the central laboratory
CMV Serology (IgG)	X																					Performed locally per SOC at the site if not previously documented within 180 days prior to Day 1.
QuantiFERON-CMV Assay	X									X				X			X			X	X	Performed by the central laboratory

Study Period	Pre-Treatment		Treatment												Follow-Up						CMV Disease and/or Early Discon Visit	Notes
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[a]**	**Day of Tp**	**D1[b]**	**W 1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**		• 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". See Footnote a for screening window.
CMV Viral Resistance Testing/gB Genotypic Testing[c, d]																				X	X	The CMV Disease Visit can occur at any time during the study. Collect these samples at CMV Disease Visit. Repeat samples should be collected at the next scheduled visit after the CMV Disease Visit.
Health Outcomes Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collect 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.
Quality of Life Assessments			X							X				X						X	X	Electronic EQ-5D and SF-36v2® (performed prior to any other procedures at the visit)
PK/Biomarkers																						
Blood for Genetic Analysis[e]	X																					
Population PK			X	X	X	X	X	X	X	X	X	X	X	X							X	Collected pre-dose in all participants at each visit of the treatment period and at CMV Disease/early discontinuation visit (if during treatment period)

Study Period	Pre-Treatment		Treatment												Follow-Up						CMV Disease and/or Early Discon Visit	Notes
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[a]**	**Day of Tp**	**D1[b]**	**W 1**	**W 2**	**W 4**	**W 6**	**W 8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**		• 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". See Footnote a for screening window.
Intensive PK at Week 1[f] (For participants of Asian descent AND participants of non-Asian descent who consent to the intensive PK study)				X																		To be collected on Study Day 6, 7, 8, 9, or 10.
Intensive PK[f] (For all participants receiving IV treatment for >5 consecutive days)				←----------X----------→																		Performed on the 6th day of IV administration

ACV = acyclovir; AE = adverse event; β-hCG = β-human chorionic gonadotropin; CMV = cytomegalovirus; D = Day, DNA= deoxyribonucleic acid; FBR = Future Biomedical Research; EQ = EuroQol; FSH = follicle-stimulating hormone; G-CSF = granulocyte colony-stimulating factor; gB = glycoprotein B; GCV = ganciclovir; HIV = human immunodeficiency virus; IEC = Independent Ethics Committee; IgG = immunoglobulin G; INR = international normalized ratio; IRB = Institutional Review Board; IV = intravenous; IVRS = interactive voice response system; IWRS = integrated web response system; LET = letermovir; LH = luteinizing hormone; NODAT = new onset diabetes mellitus after transplant; OI = opportunistic infections; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; SAE = serious adverse event; SCR = screening; SF-36v2® = 36-Item Short Form Health Survey Version 2.0; SOC = standard of care; Tp = transplant; VGCV = valganciclovir; W = Week; WOCBP = women of childbearing potential

a. Screening should begin after obtaining documented consent and may begin on the day of transplantation (ie, prior to transplantation) or as early as one 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 2) will be performed and must be completed by Day 5 post-transplant (inclusive). See Section 9.11.1 regarding details of screening procedures.

b. Start of study treatment is Day 1 (day of randomization). 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. Leftover main study plasma will be stored for FBR if the participant consents to FBR.

d. To be performed only for participants who discontinue study treatment due to suspected or confirmed CMV disease or in whom study treatment is stopped (if on study treatment) and CMV treatment is started.

e. 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 signs FBR consent.

f. Each participant will participate in the intensive PK substudy no more than twice during the study.

3. Introduction

3.1 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 5.4.1.1) and disease (ie, end-organ involvement or CMV syndrome; Section 5.4.1.1 and Appendix 7) 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 disease 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 nearly 3-fold higher among CMV seronegative (R-) kidney recipients with a transplanted kidney from CMV seropositive (D+) donor, ie, D+/R– patients (56%) compared to the incidence among D–/R+ and D+/R+ patient groups (20%; $p < 0.001$) [Husain, S., et al 2009] [Hartmann, A., et al 2006].

CMV prophylaxis is now widely used following SOT and has been associated with reductions in CMV disease, mortality, and graft rejection in high-risk patients [Humar, A., et al 2010]. Although ganciclovir (GCV) and valganciclovir (VGCV) are used for CMV prophylaxis during the post-SOT period, both GCV and VGCV are associated with myelosuppression and CMV strains resistant to GCV and VGCV have been identified [Razonable, R. R. 2013]. Although intravenous (IV) GCV is dosed based on weight, oral VGCV is prescribed in fixed doses. GCV is renally cleared, so changes in renal function may lead to over exposure and increased risk of toxicity.

There is an unmet medical need for new agents which do not cause myelosuppression, are dosed independent of renal function, and are active against both wild-type and GCV-resistant CMV.

MK-8228 (also known as letermovir, AIC246, AIC001; 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;

(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;

(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 002 is a pivotal study that will evaluate the efficacy and safety of LET versus VGCV administered as prevention of CMV disease in approximately 600 D+/R- adult kidney

transplant recipients. Study treatment will be initiated within 7 days post-transplant and continue through Week 28. After approximately 28 weeks of study therapy post-transplant, participants will be followed through Week 52 (ie, approximately 12 months post-transplant) to assess for late onset CMV disease and DNAemia (detection of CMV DNA in samples of plasma, serum, whole blood, or isolated PBLs, or in buffy-coat specimens) [Ljungman, P., et al 2016].

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.

3.2 Background

Refer to the IB/approved labeling for detailed background information on LET.

CMV continues to be the single major pathogen affecting the outcome of SOT [Eid, A. J. and Razonable, R. R. 2010]. Rates of CMV infection or disease vary depending on baseline CMV-specific immunity (ie, donor and recipient CMV immunoglobulin G [IgG] seropositivity), the overall state of post-SOT immunosuppression, and the type of organ transplant [Beam, E. 2012]. CMV infection (see also Section 5.4.1.1) may be the result of reactivation or reinfection (in CMV-seropositive recipients) or primary infection (in a CMV-seronegative recipient who received a transplant from CMV-seropositive donor) [Beam, E. 2012].

CMV disease (consisting of CMV end-organ disease and CMV syndrome, see Section 5.4.1.1 for further details) occurs most frequently between one and four months following SOT and is associated with increased morbidity, mortality as well as poor long-term outcomes following SOT [Beam, E. 2012]. 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].

The spectrum of CMV disease manifestations from CMV syndrome (ie, CMV infection with ≥2 prespecified clinical signs/symptoms and/or laboratory criteria) to CMV end-organ disease (ie, involvement of ≥1 organ system with clinical manifestations) have been described extensively (see Appendix 7; [Boeckh, M. 2011]). The most common form of CMV end-organ disease involves the gastrointestinal tract [Beam, E. 2012] [Kute, V. B., et al 2012]. Studies have shown that the risk of CMV disease in SOT is highest in CMV-seronegative recipients of CMV-seropositive donors (ie, D+R-), and in patients who receive antilymphocyte antibody therapy as pre-transplant induction or as post-transplant treatment for acute rejection [Humar, A., et al 2010].

There are currently two approaches to preventing CMV disease in SOT: prophylaxis with antivirals and pre-emptive therapy (PET), the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV DNAemia is detected

[Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S 2013]. Guidelines on the management of CMV in SOT recipients favor the use of prophylaxis over PET in the highest risk recipients [Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S 2013]. 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]. 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. 2013].

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. An effective and well-tolerated prophylactic anti-CMV medication for SOT recipients, which also has activity against CMV strains resistant to currently available agents, remains an unmet medical need.

3.2.1 Pharmaceutical and Therapeutic Background

The current standard of care (SOC) regimen for CMV prophylaxis in SOT recipients is VGCV, which has been approved for the prevention of CMV disease in kidney, heart, or kidney-pancreas transplant recipients at high risk. 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 D+/R- kidney transplant recipients [Humar, A., et al 2010].

However, VGCV is also associated with myelotoxicity as described in the VGCV label [U.S. Prescribing Information 2017]. Moreover, antiviral drug resistance, most commonly to GCV and VGCV, among CMV clinical isolates has emerged following widespread use of these drugs for prophylaxis and PET. Drug resistance is usually seen after treatment duration with antiviral agents of weeks to months [Beam, E. 2012]. The majority of resistance mutations to GCV and VGCV are associated with mutations in the UL97 encoded viral protein kinase [Lurain, N. S. and Chou, S. 2010]. Resistance to GCV and VGCV also occurs via mutations in the viral deoxyribonucleic acid (DNA) polymerase gene (UL54), often in the presence of UL97 mutations [Boivin, G., et al 2012].

LET is an anti-CMV agent with a novel mechanism of action. LET inhibits the viral terminase complex (UL51/UL56/UL89), an enzyme that plays an important role in cleavage of concatenated viral DNA into individual unit-length genomes that are subsequently inserted into CMV procapsids to generate infectious CMV virions [Goldner, T., et al 2011]. LET has demonstrated potent, selective, and reversible inhibition of CMV activity in preclinical

studies in vitro and efficacy against the virus in vivo [Lischka, P., et al 2010] [Goldner, T., et al 2011].

LET has been shown to be generally well tolerated in 28 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 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 efficacy and safety of LET versus VGCV in prevention of CMV disease in adult D+/R- kidney transplant recipients.

3.3 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.

4. Objectives/Hypotheses and Endpoints

In adult D+/R- (ie, CMV seropositive organ donor/CMV seronegative organ recipient) kidney transplant recipients:

Objective/Hypothesis	Endpoint
Primary	

• Objective: To evaluate the efficacy of LET versus VGCV, as measured by the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant.
  • Hypothesis (H1): LET is non-inferior to VGCV in the prevention of CMV disease through 52 weeks post-transplant.
  • Hypothesis (H2): LET is superior to VGCV in the prevention of CMV disease through 52 weeks post-transplant. Hypothesis testing will be performed only if non-inferiority is demonstrated.
	• CMV disease (see Section 5.4.1.1)

Secondary	
• Objective: To evaluate the efficacy of LET versus VGCV, as measured by the proportion of participants with adjudicated CMV disease through 28 weeks post-transplant.	• CMV disease (see Section 5.4.1.1)
• Objective: To evaluate the efficacy of LET versus VGCV, as measured by the time to onset of adjudicated CMV disease through 52 weeks post-transplant.	• Time to onset of adjudicated CMV disease through 52 weeks post-transplant
• Objective: To evaluate the safety and tolerability of LET versus VGCV.	• Accumulated safety data (adverse events, laboratory, vital signs, etc.)
Exploratory	
• Objective: To evaluate the proportion of participants with quantifiable CMV DNAemia in LET versus VGCV as measured by the central laboratory through 28 weeks post-transplant and 52 weeks post-transplant.	• Quantifiable CMV DNAemia (see Section 5.4.1.1.1)
• Objective: To evaluate the proportion of participants who develop leukopenia and neutropenia in LET versus VGCV during the treatment phase.	• Laboratory and AE indications of leukopenia and neutropenia (see Section 10.4.2)

Objective/Hypothesis	Endpoint
• Objective: To evaluate the proportion of participants experiencing allograft dysfunction and/or rejection in LET versus VGCV through 28 weeks post-transplant and 52 weeks post-transplant.	• Allograft dysfunction and/or rejection (see Section 10.4.3)
• Objective: To evaluate the incidence of new onset diabetes mellitus after transplant (NODAT) in LET versus VGCV through 28 weeks post-transplant and 52 weeks post-transplant.	• NODAT (see Section 5.4.1.1.2)
• Objective: To evaluate health outcomes in LET versus VGCV through 28 weeks post-transplant and 52 weeks post-transplant.	• Health outcomes (see Section 10.4.3)
• Objective: To evaluate the antiviral resistance to LET in prophylaxis failures through 52 weeks post-transplant.	• Antiviral resistance to LET in prophylaxis failures (see Section 9.5.8.3)
• Objective: To explore the relationship between CMV glycoprotein B (gB) genotype and response to the treatments administered	• See Section 9.5.8.4 for details.
• Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. a. Variation across the human genome will 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 analyses (see Section 5.4.1.5 for details)
• Objective: To evaluate patient-reported outcomes in LET versus VGCV through 52 weeks post-transplant.	• EuroQol (EQ)-5D and 36-Item Short Form Health Survey Version 2.0 (SF-36v2®) scores
• Objective: To evaluate the pharmacokinetics of LET.	• Pharmacokinetic endpoints (see Section 10.6.3.2 for details).

5. Study Design

5.1 Overall Design

This is a randomized, active-controlled, multi-site, double-blind (with in-house blinding) study to evaluate the efficacy and safety of LET versus VGCV in the prevention of CMV disease in adult kidney transplant recipients with a negative CMV IgG serostatus who received a kidney transplant from a donor with a positive CMV IgG serostatus (D+/R–). This study will be conducted in conformance with Good Clinical Practices. The definition of CMV disease is provided in Section 5.4.1.1.

Approximately 600 D+/R- kidney transplant recipients will be randomized in a 1:1 ratio to receive LET or VGCV within 7 days post-transplant.

LET Arm

From Day 1 (day of randomization) through Week 28, participants in the LET treatment arm will receive:

- LET 480 mg once daily (QD) given orally (either as one 480 mg tablet or two 240 mg tablets, based on participant's swallowing capability at the site investigator's discretion), or, if the participant is receiving concomitant cyclosporin A (CsA), LET 240 mg QD given orally.
- Placebo to VGCV given orally.
- Acyclovir* (ACV) 400 mg** given orally (supplied as capsule or tablet) every 12 hours for prophylaxis against herpes simplex virus (HSV) and varicella zoster virus (VZV).

VGCV Arm

From Day 1 through Week 28, participants in the VGCV treatment arm will receive:

- Placebo to LET given orally
- VGCV 900 mg QD** (given orally as two 450 mg tablets)
- Placebo to ACV given orally

The above (LET arm and VGCV arm) assumes:

- Participants can tolerate swallowing and/or does not develop a condition that may interfere with the absorption of the oral formulation (see Section 7.1 for details regarding IV dosing).
- That the renal function as measured by creatinine clearance (CrCl) is ≥60 mL/min (see Section 7.2 for details on CrCl-based dose adjustments).

Note: The antiviral activity of LET is specific for CMV, while VGCV has anti-CMV, as well as anti-HSV and anti-VZV activities. Since patients receiving VGCV for CMV prophylaxis for ≥100 days typically do not receive additional agents for HSV/VZV prevention, ACV is provided to participants in the LET arm from Day 1 through Week 28 (ie, ~200 days) [Pergam, S. A. 2009] [Wilck, M. B. 2013]. Therefore, participants in the LET and VGCV arms will receive ACV for HSV and VZV prophylaxis and matching placebo from Day 1 through Week 28, respectively.

** Acyclovir and Aciclovir are equivalent generic names.*

***Dose adjustments of VGCV, GCV, and ACV based on CrCl are provided in Section 7.2. There are no dose adjustments of LET based on CrCl.*

If participants in the LET treatment arm 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 randomization/Day 1, then such participants can receive an IV formulation of LET. Participants on concomitant CsA will receive 240 mg IV LET QD, while participants not on concomitant CsA will be randomized 1:1 to receive either 240 mg IV LET QD or 480 mg IV LET QD, as well as IV ACV (see Section 7.2 for IV ACV dosing). Participants randomized to receive either 240 mg IV LET or 480 mg IV LET without concomitant CsA will receive 480 mg of oral formulation of LET when they are able to tolerate oral formulation of LET, and if unable to tolerate the oral formulation at a later time point in the study, will receive the same dose of IV LET (either 240 mg QD or 480 mg QD) to which they were randomized to receive earlier in the study.

Participants in the VGCV treatment arm who cannot tolerate swallowing and/or have a condition that may interfere with the absorption of the oral formulation at or after randomization/Day 1 will receive a comparable prophylaxis dose of IV GCV at 5 mg/kg QD, as well as IV ACV matching placebo.

Randomized participants will be stratified by the use or non-use of highly cytolytic anti-lymphocyte immunotherapy during induction; such highly cytolytic anti-lymphocyte immunotherapy is associated with increased risk for CMV infection (Sections 3.2 and 5.4.1.1) (see Section 7.3.1 for further details).

After completion of study therapy at Week 28, participants will continue to be followed for efficacy, safety, 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 Schedule of Activities (SoA) (Section 2). All scheduled study visits will be completed regardless of when cessation of study treatment occurs.

Key aspects of the proposed study are described in the remainder of Section 5 (Study Design), as well as Sections 6-9 (Study Population, Treatments, Discontinuation/Withdrawal Criteria, and Study Assessments and Procedures).

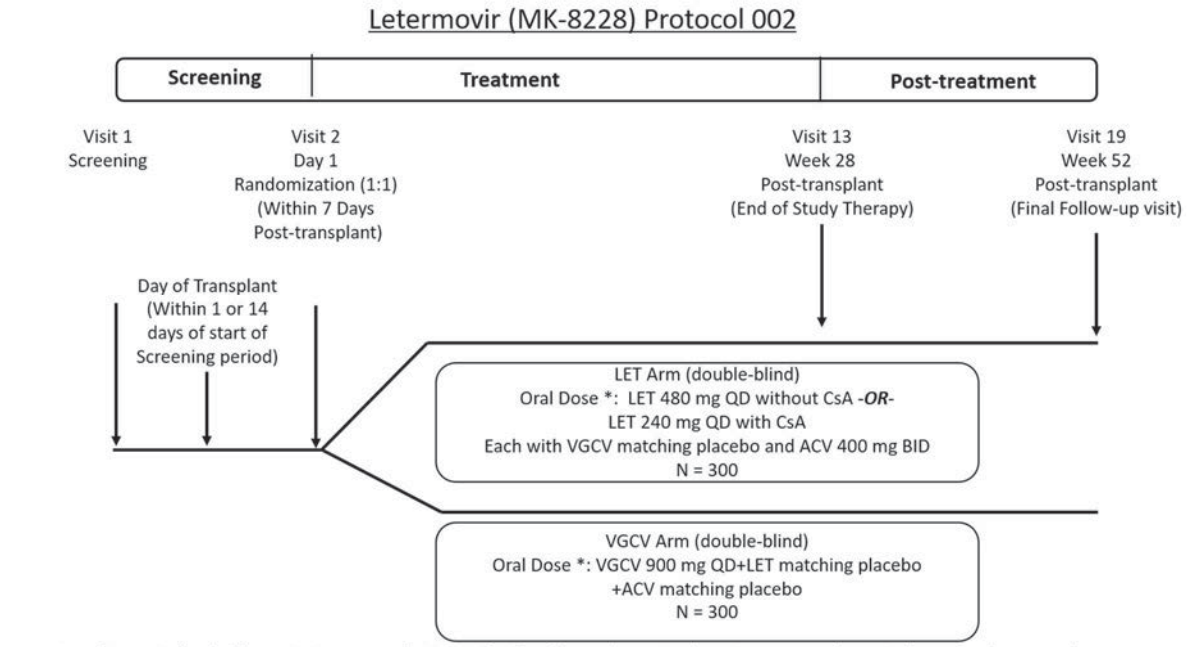
For ongoing safety evaluations and to ensure safe study conduct, an independent unblinded external Data Monitoring Committee (DMC) will be established. The DMC will not review CMV DNA polymerase chain reaction (PCR) results or perform any planned efficacy analysis but can be provided with efficacy data (upon request by the DMC) to support the benefit-risk assessment. Specific details regarding the DMC will be described in the DMC charter (see Appendix 3 for additional details).

An independent blinded Clinical Adjudication Committee (CAC) will be established for this study to adjudicate all potential CMV disease cases, as identified by site investigators or as otherwise described in the CAC charter (see Section 5.4.1.1.1 and Appendix 3).

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Study Diagram

The study design is depicted in Figure 1.



Screening of potentially eligible participants may begin on the day of transplantation (ie, prior to transplantation) or as early as one 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.

Dose of ACV, VGCV, and GCV will be modified based on creatinine clearance, see Section 7.2.

* If participants are unable to tolerate swallowing of tablets after randomization, then (in a blinded manner) IV formulations may be administered as follows: LET arm: IV LET 480 mg QD without CsA or 240 mg QD without CsA or 240 mg QD with CsA and IV ACV 250 mg/m^2 BID; VGCV arm: IV GCV 5 mg/kg QD and IV ACV matching placebo BID

ACV = acyclovir; BID = twice daily; CsA = cyclosporine A; GCV = ganciclovir; IV = intravenous; LET = letermovir; QD = once daily; VGCV = valganciclovir

Figure 1 MK-8228-002 Study Design

5.2 Number of Participants

Approximately 600 participants will be randomized (see Section 10.9).

5.3 Beginning and End of Study Definition

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

5.3.1 Clinical Criteria for Early Study Termination

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

Based on recommendations from the external DMC, the Executive Oversight Committee (EOC) determines that the extent (incidence and/or severity) of emerging adverse effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

As stated in Section 3.2.1, the current SOC for CMV prophylaxis in D+/R- kidney transplant recipients is the administration of VGCV during the 200-day post-transplant period. Several studies of VGCV in this patient population have been conducted; therefore, the CMV disease event rate is well characterized [Humar, A., et al 2010] [Paya, C., et al 2004].

Accordingly, Protocol 002 is a non-inferiority study of LET versus VGCV and the primary efficacy endpoint is:

- The proportion of participants with adjudicated CMV disease through 52 weeks post-transplant.

The key secondary efficacy endpoints of the study are:

- The proportion of participants with adjudicated CMV disease through 28 weeks post-transplant.

- Time to onset of adjudicated CMV disease through 52 weeks post-transplant.

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 7) 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:
        - Proven CMV end-organ disease
        - Probable CMV end-organ disease.
- CMV syndrome (full list of criteria and clinical definition in Appendix 7) 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 7.

5.4.1.1.1 CMV Based Assessments

CMV DNA Measurements

Evidence of quantifiable CMV DNAemia is included as an exploratory analysis 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 150 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

Documented quantifiable CMV DNAemia is defined as any detected CMV with a numeric value and does not include reporting of PCR results as "detected, not quantifiable." Additional details on CMV DNA PCR testing are described in Section 9.5.8.2.

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, blinded 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 primary and secondary efficacy endpoints.

Adjudication of CMV disease cases by an established CAC will standardize the CMV disease diagnosis for the primary and 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 2). 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 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.

5.4.1.1.2 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].

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].

Participants developing NODAT (as identified by the site and also as identified by a confirmatory analysis) will be analyzed (Section 10). 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 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 (Section 10) [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, above, 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 randomization (ie, such hypoglycemic agents that are not listed as prior medications and newly identified as a concomitant medication during the study).

5.4.1.1.3 Rationale for Non-Inferiority Margin

The 10% non-inferiority margin used in this study is based on the preservation of the majority of efficacy (>50%) of VGCV compared to placebo in preventing CMV disease after renal transplantation under a number of scenarios.

From the VGCV label for 200-day treatment, the CMV disease rate at 12 months post-transplant in the VGCV group was 16.8% (26 out of 155), which corresponds to a disease-free rate of 83.2% with a 95% confidence interval (CI) of (76.4%, 88.7%). The proportion of participants with CMV disease in a placebo group at 12 months post-transplant was extrapolated from Lowance, et al. [Lowance, D., et al 1999], which showed that the CMV disease rate was 45% at 90 days after renal transplantation (corresponding to a disease-free rate of 55%). Since it is expected that more cases of CMV disease would occur between 90 days and 12 months post-transplant, it is reasonable to assume the disease-free rate in a placebo group at 12 months post-transplant is 50% or less.

Table 1 shows the percent of efficacy retained in this study using a 10 percentage point margin for a range of disease-free rates consistent with the above assumptions for the VGCV and placebo groups. The percent retained was based on the lower bound of the 95% CI of difference in the disease-free rate (VGCV - Placebo), assuming 300 participants per group. For example, in the scenario where the VGCV disease-free rate = 90% and the placebo disease-free rate = 50%, the 95% two-sided CI for the VGCV rate (270/300) minus the placebo rate (150/300) is (33%, 46%) using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. A 10 percentage point non-inferiority margin would indicate that the lower bound for this difference in the study could be as low as 23% (33% minus 10%); thus, the percent retained would be 23/33 = 69.7%.

This is a conservative approach since the lower bound of the 95% CI was used as the historical effect and a range of possible placebo rates were used in the calculations. In the majority of scenarios in Table 1, more than 50% of the efficacy is retained using the 10 percentage point margin. Thus, a 10 percentage point margin is proposed in this study.

Table 1 Percentage of Efficacy Retained with 10 percentage point Margin (n = 300/arm)

VGCV Disease-free Rate	Placebo Disease-free Rate			
	0.50	**0.45**	**0.40**	**0.35**
0.9	69.7%	73.7%	76.7%	79.2%
0.85	64.3%	69.7%	73.7%	76.7%
0.8	56.5%	64.3%	69.7%	73.7%
0.75	41.2%	54.5%	63.0%	68.8%
VGCV = valganciclovir				

5.4.1.2 Patient-reported Outcome Endpoints

Successful kidney transplantation is often judged by the impact on morbidity and mortality, but these measures do not capture the full extent of the impact on patients' life and well-being. Patient-reported outcomes (PROs) measuring health-related quality of life (QoL) can fill this gap and provide a more complete evaluation of the impact of a kidney transplant procedure on a patients' health [Acquadro, C., et al 2003] [Szende, A., et al 2005]. Post-transplant complications and toxicities resulting from drugs commonly used in the transplant process can have a negative effect on a patients' QoL. Patient-reported outcomes (PROs) have been used extensively to study various immunosuppressive regimens in kidney transplant, particularly where use of these drugs can result in drug toxicities or other complications that are not life-threatening but occur frequently and are burdensome to patients [Cleemput, I. 2007].

The EuroQoL (EQ)-5D, a validated tool of PROs, is a general measure of QoL that has been used frequently in kidney transplant and plays an important role in providing utility estimates for economic modeling [Cleemput, I., et al 2004]. The 36-Item Short Form Health Survey Version 2.0 (SF-36v2®) is a generic health survey which includes 36 questions to measure functional health and well-being from the participant's perspective and has been validated in kidney transplant patients [Barotfi, S., et al 2006]. The QoL questionnaires will be collected/performed at the timepoints indicated in the Study SoA (see Section 2).

5.4.1.3 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 Study SoA (Section 2). Serum Inhibin B, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels in male participants will be collected to monitor testicular function. Adverse events are evaluated and recorded according to Section 9.3. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

Leukopenia and Neutropenia

An evaluation of the safety and tolerability of LET, as assessed by review of the accumulated safety data, will be assessed as an endpoint in this study. For the safety analysis, leukopenia and neutropenia reported as AEs during the treatment period and also using prespecified laboratory parameter limits (see below) will be used for analysis (Section 10).

For each episode of leukopenia or neutropenia that is reported as an AE during the treatment period, the corresponding laboratory values and normal ranges of total white blood cell (WBC) and absolute neutrophil count (ANC) will be collected (ie, local and central laboratory values).

- If the AE of leukopenia or neutropenia was reported based on local laboratory results collected at the discretion of the investigator during non-study visits, such local laboratory results and corresponding normal range values will be collected for analysis.

- If the AE of leukopenia or neutropenia was reported based on central laboratory values of total WBC and ANC collected at a scheduled study visit, then such corresponding central laboratory values will be analyzed.

Sex Hormone Analysis

The rationale for analyzing sex hormone levels is as follows:

- Preclinical repeat-dose toxicity studies and fertility studies of LET in male rats revealed non-reversible testicular degeneration and reduced male fertility indices with LET at high dose levels. These findings were not observed in studies in mice (in studies up to a 3-month duration) or monkeys (in studies up to a 9-month duration) where higher systemic exposures were obtained, suggesting that the testicular findings in rats may be specific for this species. The relevance to humans is unknown.

- In order to evaluate the potential risk for testicular toxicity associated with LET in human subjects, levels of serum Inhibin B, LH, FSH, and testosterone as markers of testicular toxicity were evaluated in male participants in the Phase 3 trial (P001) to monitor changes in testicular function from baseline 04XH3T. These serum biomarkers have been used to monitor gonadotoxicity in subjects who received antineoplastic chemotherapy [Muller PY and Dieterle F 2009] and are also listed as hormones that may help to inform the drug's effect on testicular function in the United States Food and Drug Administration (US FDA) guidance document on testicular toxicity and evaluation during drug development [U.S. Food and Drug Administration 2015]. The proportion of participants with low, normal, or high levels of serum Inhibin B, LH, FSH, and testosterone in male participants at Baseline and the shift from baseline at the End-of-Treatment and Week 24 post-transplant visit was evaluated in P001 by treatment arm. There was no clinically relevant effect of LET on male sex hormones in a participant population of allogeneic HSCT recipients.

In this study, serum Inhibin B, LH, FSH, and testosterone levels will be measured in all male participants. The central laboratory based sex hormone results will not be shared with the respective site investigators.

5.4.1.4 Pharmacokinetic Endpoints

Pharmacokinetic (PK) samples will be collected from all participants as described in the Study SoA (Section 2). The intensive and population PK data will be used to characterize the PK of LET in kidney transplant recipients and evaluate exposure-response relationships with selected efficacy and safety endpoints.

LET has a complex PK profile with non-linearity observed over the clinical dose range and also small differences were observed in exposures between Asians versus non-Asians (eg, 33.2% higher in Asians versus whites). As such, PK samples from a sufficient number of participants will be needed to characterize PK and identify clinically relevant covariates.

Population PK will be collected in all participants pre-dose (a single sample per subject within 0-2 hours prior to dose) at each visit of the treatment period.

Intensive PK will be collected during the study as follows:

Week 1 intensive PK:

- ALL participants of Asian descent
    - Based on the proportion of participants who were of Asian descent (<10%) in P001 (defined as a participant who self-reports both parents as being of Asian heritage, ie, the parents should trace their heritage to one of the following countries: Brunei, Cambodia, East Timor, Indonesia, Japan, Laos, Malaysia, Mongolia, Myanmar (Burma), Korea, People's Republic of China, Philippines, Singapore , Taiwan, Thailand, or Vietnam), intensive PK (at the Week 1 visit; see below and Section 2) from all Asian participants for a robust assessment of PK and ethnic differences will be needed for this study. Such intensive PK sampling will occur regardless of the study drug formulation (IV or oral) administered at the Week 1 visit.
    - Week 1 intensive PK will be performed pre- and post-dose at any time between Study Day 6-10 (inclusive) for participants of Asian descent.
- OPTIONAL for additional participants (up to ~60 participants of non-Asian descent or up to 10% of the non-Asian study population) who consent to Week 1 intensive PK regardless of study drug formulation (IV or oral) prior to or at the Week 1 visit to obtain additional PK data in the kidney transplant population.
    - Week 1 intensive PK will be performed pre- and post-dose at any time between Study Day 6-10 (inclusive) for consenting participants of non-Asian descent.

Intensive PK during IV administration of study medication:

- ALL participants who receive >5 consecutive days of IV therapy will have intensive PK on the 6th day of IV (prior to and after the 6th day dose) – no more than ONCE during the entire study, regardless of how many times the IV therapy criterion is fulfilled during the study.
    - No participant will have more than 1 intensive PK performed during the first 2 weeks of the study.
    - If a participant qualifies for the intensive PK at the Week 1 visit (see above and Section 2) and also qualifies for intensive PK due to >5 consecutive days of IV therapy within the first two weeks of the study, then intensive PK will only be performed on the first qualifying event. If the events coincide on the same day (eg, the Week 1 visit), the intensive PK will still only be collected at the Week 1 visit (see above and Section 2).

Based on the above, participants may qualify for and undergo no more than two intensive PK measurements during the study: at Week 1 (see above) and on the 6th day after 5 consecutive days of IV therapy (also see above).

Table 2 summarizes the requirements of population PK and intensive PK collection during the study.

Table 2 Population Pharmacokinetic and Intensive Pharmacokinetic Collection

	Population PK – Pre-dose at Each Visit of Treatment Period	**Intensive PK at Week 1 Visit (Oral or IV Administration)**	**Intensive PK (IV Administration >5 consecutive days)**
All Participants (Asian and Non-Asian)	X (Mandatory)		X (Mandatory)
Asian Participants		X (Mandatory)	
Optional Consenting Non-Asian Participants		X (Optional)	
All participants who receive >5 consecutive days of IV therapy will have intensive PK on the 6th day of IV (prior to and after the 6th day dose) – no more than ONCE during the entire study, regardless of how many times the IV therapy criterion is fulfilled during the study. Participants may qualify for and undergo no more than two intensive PK measurements during the study: at Week 1 and on the 6th day after 5 consecutive days of IV therapy. IV = intravenous; PK = pharmacokinetics			

Details of planned analyses of PK measurements are in Section 10.6.3.2.

5.4.1.5 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, and 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 will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses 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 be specifically investigated for PK variability, as well as efficacy and AEs.

5.4.1.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (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 trial) 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 this Future Biomedical Research sub-trial are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

5.4.2 Rationale for the Use of Comparator (Valganciclovir and Ganciclovir)

In the setting of kidney transplant, the SOC for prevention of CMV disease is VGCV at an oral dose of 900 mg QD to be started within 10 days of transplantation until 28 weeks (ie, 200 days) post-transplant [Humar, A., et al 2010].

Both VGCV and GCV are approved for the prevention of CMV disease following SOT and are associated with myelotoxicity. GCV has been available in both IV and oral formulations and was studied in heart transplant and HSCT recipients. The oral formulation of GCV is associated with low oral bioavailability and high pill burden (1 g × three times a day dose) and is not currently available. VGCV is a prodrug of GCV with improved bioavailability compared with oral GCV. VGCV is indicated for the prevention of CMV disease in kidney, kidney-pancreas, and heart transplant patients, at the 900 mg QD oral dose. Therefore, VGCV (and IV GCV, if intolerant of oral medications) has been chosen as the comparator for this study.

5.5 Justification for Dose

5.5.1 Starting Dose for This Trial

This clinical study will evaluate:

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

versus

- VGCV oral 900 mg QD (see Section 7.2 for comparable IV dose of GCV).

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 28 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 240 mg QD to 480 mg QD. In the Phase 2b study (Protocol 020 (P020), AIC246-01-II-02), 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 approximately 3-fold. 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 [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.

LET has previously been evaluated in a Phase 3 trial in HSCT recipients at doses of 240 mg PO or IV when administered with CsA, and 480 mg PO or IV when administered without CsA. All doses were generally well-tolerated and efficacious; however, LET exposures (steady state median AUC) in HSCT recipients with the 480 mg IV dose (without CsA) were higher than in the other three dose groups. Population PK simulations using data from the Phase 3 trial in HSCT recipients suggest that a 240 mg IV dose (without CsA) will provide exposures comparable to exposures obtained following administration of a 480 mg PO dose (without CsA). Therefore, an additional dose group of 240 mg IV (without CsA) was added to the current protocol to evaluate the PK, efficacy, and safety of this dose in transplant recipients. Participants who receive IV LET (without CsA) will be randomized 1:1 to receive either a 480 mg or 240 mg dose.

Rationale for Dose of VGCV and GCV

In the setting of kidney transplant, the SOC for prevention of CMV disease is VGCV at an oral dose of 900 mg QD to be started within 10 days of transplantation until 28 weeks (ie, 200 days) post-transplant [Humar, A., et al 2010].

If participants in the VGCV arm cannot tolerate oral medications, IV GCV 5 mg/kg QD will be administered [U.S. Prescribing Information 2017].

See Section 5.4.2 for further details.

5.5.2 Maximum Dose/Exposure for This Trial

Rationale for Treatment Duration

CMV prophylaxis is now widely used in the transplant setting and 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 results of the recent IMPACT study (Section 3.2) confirm that the incidence of CMV disease at 12 months post-transplant can be significantly reduced if a 6-month prophylaxis course is implemented instead of a 3-month course. 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 [Humar, A., et al 2010]. Participants will be followed through Week 52 to evaluate the incidence of late-onset CMV disease after the conclusion of study medication.

6. Study Population

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

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

6.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Have a documented negative serostatus for CMV (ie, recipient CMV IgG seronegative [R-]) within 180 days prior to randomization.

2. Anticipate receiving a primary or secondary allograft kidney from a CMV IgG seropositive (D+) donor at the time of screening AND have received a primary or

secondary allograft kidney from a documented D+ donor at the time of randomization.

a. 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.

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

Demographics

4. Be ≥18 years of age on day of signing informed consent.

Male Participants

5. A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.

   Note: A male participant who has a pregnant partner at enrollment will not be included in the study.

Female Participants

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

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

      OR

   b. A WOCBP who agrees to follow the contraception guidance in Appendix 5 during the treatment period and for at least 90 days after the last dose of study treatment.

Informed Consent

7. Understand the study procedures, alternative treatment available, and risks involved with the study, and he/she voluntarily agrees to participate by giving written informed consent and is willing to adhere to dose and visit schedules. Participant may also provide consent for Future Biomedical Research. However, the participant may participate in the main study without participating in Future Biomedical Research.

Other

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

6.2 Exclusion Criteria

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

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 randomization.

4. Has suspected or known hypersensitivity to active or inactive ingredients of LET formulations, VGCV, GCV, and/or ACV formulations.

5. Is on dialysis or plasmapheresis at the time of randomization.

   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 randomization; and (2) is expected to remain off dialysis or plasmapheresis may be enrolled, provided that all other inclusion/exclusion criteria are met.

6. Has post-transplant renal function of CrCl ≤10 mL/min at randomization (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 randomization 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 randomization. If the repeat value meets this exclusion criterion again, such participants may NOT continue in the screening/randomization process. Only the laboratory test with specific out-of-range value (and not the entire laboratory panel) should be repeated.

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

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

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

8. Has both moderate hepatic insufficiency AND moderate-to-severe renal insufficiency at screening.

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

9. Has any uncontrolled infection on the day of randomization.

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

11. Requires mechanical ventilation, or is hemodynamically unstable, at the time of randomization.

12. 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.

13. Is pregnant or expecting to conceive, is breastfeeding, or plans to breastfeed from the time of consent through at least 90 days following cessation of study therapy.

14. Is expecting to donate eggs or sperm starting from the time of consent through at least 90 days following cessation of study therapy.

15. 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.

16. Has exclusionary laboratory value at screening, as listed in Table 3.

Table 3 Laboratory Exclusion Criteria

Laboratory Assessment	Exclusionary Value
CMV serology (IgG)	Positive
Hemoglobin	<8 g/dL
Platelets	<25,000 cells/µL
Absolute neutrophil count	<1,000 cells/µL
Total bilirubin	>2.5 × ULN
ALT	>5 × ULN
AST	>5 × ULN
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; IgG = immunoglobulin G; ULN = upper limit of normal	

Prior/Concomitant Therapy

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

    a. Cidofovir

    b. CMV hyper-immune globulin

    c. Any investigational CMV antiviral agent/biologic therapy.

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

    d. LET

    e. GCV

    f. VGCV

    g. Foscarnet

    h. ACV (at doses >3200 mg PO per day or >25 mg/kg IV per day)

    i. Valacyclovir (at doses >3 g PO per day)

    j. Famciclovir (at doses >1500 mg PO per day)

    Note: The exclusion of LET, GCV, and VGCV applies to prior use and no additional unblinded use of LET, GCV, or VGCV outside of the context of the study.

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.

    Note: Participants with a history of marijuana use which is not deemed excessive by an investigator or does not interfere with the participant's daily function may participate in the study but must be instructed to discontinue any further use of recreational marijuana prior to entry into study and throughout the study period.

20. Is taking or plans to take any of the prohibited medications listed in the protocol (see Section 7.7).

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 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.

6.3 Lifestyle Restrictions

No lifestyle restrictions are required based on study procedures.

6.3.1 Meals and Dietary Restrictions

Study therapy should be taken with food, as described in Section 9.1.9.1.

Participants must avoid consumption of grapefruit, Seville oranges or their respective juices, and other quinine-containing drinks or food during the study from 2 weeks prior to study treatment administration until 72 hours after the final administration of study treatment.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/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 adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

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

7. Treatments

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

7.1 Treatments Administered

The study treatments to be used in this trial are outlined below in Table 4 and Table 5. In this study, approximately 600 participants will be randomized in a 1:1 ratio as follows: approximately 300 participants will receive LET, placebo to VGCV, and ACV through Week 28 and approximately 300 participants will receive VGCV, placebo to LET, and placebo to ACV through Week 28.

The oral and IV formulations of LET, ACV, and VGCV (and the corresponding IV formulation of GCV) that will be administered in this study are outlined below in Table 4 and Table 5, respectively. Since VGCV tablets are recommended to be taken with food, study therapy in both treatment arms should be taken with food.

Participants requiring the oral 480 mg dose of LET should be initiated with one 480 mg tablet (LET or matching placebo). In the event a participant is unable to swallow the 480 mg tablet, study therapy may be initiated with 2 × 240 mg tablets (LET or matching placebo). Participants who are initiated with two tablets of the 240 mg LET or matching placebo should continue with that regimen. If the 480 mg tablet is not available based on country-specific requirements or is not available at the site for any other reason, 2 × 240 mg tablets should be used for the 480 mg dose.

For participants who cannot tolerate swallowing and/or develop a condition that may interfere with the absorption of the oral formulation at or after randomization/Day 1, study therapy can be initiated/switched to the IV formulation. Use of the IV formulation should generally be limited to 4 weeks or less in duration per participant. However, it will be left to the investigator's discretion to continue IV administration beyond 4 weeks, if the benefit/risk ratio supports continued administration. Simultaneous use of IV and oral study therapy is **not** allowed. 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.

For weight-based dosing of GCV and body surface area (BSA) calculations for IV ACV dosing, the most recently measured total body weight (kg) as part of standard of care should be used (additional details provided in the Pharmacy Manual).

Table 4 Study Treatments – Oral Formulation

	LET			**VGCV**		**ACV**	
	LET (for Participants not on CsA)	**LET (for Participants on CsA)**	**Placebo to LET**	**VGCV**	**Placebo to VGCV**	**ACV (for Participants in the LET Arm)**	**Placebo to ACV (for Participants in the VGCV Arm)**
Dose /Potency	480 mg (one 480-mg tablet or two 240-mg tablets)	240 mg tablet	NA	900 mg (Two 450-mg tablets)	NA	400 mg capsule or 400 mg tablet	NA
Dose Frequency	QD	QD	QD	QD	QD	Every 12 hours	Every 12 hours
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Regimen/Treatment Period	Through Week 28	Through Week 28	Through Week 28	Through Week 28	Through Week 28	Through Week 28	Through Week 28
Use	Experimental	Experimental	NA	Active comparator	NA	Prophylaxis against HSV and VZV	NA
Sourcing	Centrally	Centrally	Centrally	Centrally	Centrally	Centrally	Centrally

Dose of ACV and VGCV will be modified based on creatinine clearance, see Section 7.2.

ACV = acyclovir; CsA = Cyclosporin A; HSV = herpes simplex virus; LET = letermovir; NA = not applicable; QD = once daily; VGCV = valganciclovir; VZV = varicella zoster virus

Table 5 Study Therapy – IV Formulation (For Participants Who Cannot Tolerate Oral Formulation at and/or After Randomization)

	LET		GCV	ACV	
	LET (for Participants not on CsA)	**LET (for Participants on CsA or not on CsA)**	**GCV**	**ACV (for Participants in the LET Arm)**	**Placebo to ACV (for Participants in the VGCV Arm)**
Dose/ Potency	480 mg	240 mg	5 mg/kg	250 mg/m^2	NA
Dose Frequency	QD	QD	QD	Every 12 hours	Every 12 hours
Route of Administration	Intravenous*	Intravenous*	Intravenous*	Intravenous*	Intravenous*
Regimen/Treatment Period	Through Week 28**	Through Week 28**	Through Week 28**	Through Week 28**	Through Week 28**
Use	Experimental	Experimental	Active-comparator	Prophylaxis against HSV and/or VZV	NA
Sourcing	Centrally (blinding done by site)	Centrally (blinding done by site)	Centrally (blinding done by site)	Centrally (blinding done by site)	Locally***

Dose of ACV and GCV will be modified based on creatinine clearance, see Section 7.2.

ACV = acyclovir; CsA = Cyclosporin A; HSV = herpes simplex virus; IV = intravenous; LET = letermovir; NA = not applicable; QD = once daily; VZV = varicella zoster virus

* The IV formulation dosing volume of LET is 250 mL and the duration of infusion will be 60 minutes. To reduce the risk of unblinding, the infusion volume of GCV IV formulation will be 250 mL and dosed at 5 mg/kg body weight and duration of infusion will be 60 minutes. The IV formulation of ACV (or matching IV placebo) will be 250 mL and dosed at 250 mg/m^2 body surface area (BSA) and duration of infusion will be 60 minutes. The maximum concentration of ACV for IV infusion is not to exceed 7 mg/mL as specified per the product label.

** 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.

*** The type of placebo and diluent for the IV formulation of ACV are described in the Pharmacy Manual.

If the participant fulfills all inclusion criteria and does not meet any exclusion criteria for the study, then the participant should begin study therapy on the day of randomization, which will be within the first 7 days (inclusive) post-transplant. The total duration of therapy is approximately 28 weeks during which any interruptions of study therapy may not exceed >7 consecutive days.

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

All supplies indicated in Table 4 and Table 5 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 9.1.9 for details regarding administration of the study treatment.

7.2 Dose Modification (Escalation/Titration/Other)

Both oral (tablet) and IV formulations of LET (and matching placebo) will be available. For additional details on IV or oral formulations of LET dosing, see Section 5.1. The distribution of blinded oral study therapy and blinded IV study therapy with respect to concomitant CsA use is described in Table 10 and Table 11, respectively. For additional details on adjustments to LET dosing based on the status of concomitant CsA administration (eg, interruption or stopping) see Section 9.11.2.2.

The IV formulation of LET contains the excipient hydroxypropyl betadex. Cyclodextrins can cause nephrotoxic effects in animals at systemic exposure; however, there is currently no evidence of these effects in humans. Hydroxypropyl betadex amounts of approximately 250 mg/kg/day for 21 days were found to be safe in humans older than 2 years [European Medicines Agency 2014]. Given this tolerability information in humans and the amount of cyclodextrin (3600 mg) contained in the highest dose (480 mg) of the IV formulation of LET administered in P001, nephrotoxic effects due to cyclodextrin were not expected in the trial population of adult HSCT recipients. Data from P001 suggest that the use of the cyclodextrin-containing IV formulation in this trial was not associated with renal toxicity and that dosing with the IV formulation is justified throughout the duration of therapy [Marty, F. M., et al 2017].

Based on the above, the use of IV LET is permitted in participants with renal insufficiency, provided CrCl is >10 mL/min. However, for this study in renal transplant participants, the 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 randomization/Day 1. Participants on IV LET should be switched to the oral formulation (ie, at the next planned dose) as soon as they are able to swallow and/or the condition that warranted the use of the IV formulation has resolved.

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, the changes observed in LET exposures in participants with moderate or severe renal impairment are within the clinical comparability bounds and no dose adjustment is recommended for participants with moderate or severe renal impairment [Kropeit, D., et al 2017].

Participants will be randomized to receive LET (480 mg oral LET, or 240 mg oral LET if concomitantly given with CsA), or 900 mg VGCV (two 450 mg tablets) PO once daily provided that the participant has normal renal function (ie, CrCl of ≥60 mL/min based on Table 6). Dose modification of study medications due to reasons other than reduced renal function (eg, leukopenia and/or neutropenia) is not permitted. If a participant initiates

treatment with CsA at any time during the study therapy period (ie, through Week 28), then the LET dose should be decreased to 240 mg QD. If a participant discontinues CsA during the study therapy period for more than 3 consecutive days, then LET should be increased to 480 mg QD.

For participants with reduced renal function, the dose of VGCV (or IV GCV) or ACV will be modified, based on CrCl (using Cockcroft-Gault formula) according to Table 6 (VGCV), Table 7 (GCV), Table 8 (oral ACV), and Table 9 (IV ACV). Dose modification of study medications due to reasons other than reduced renal function (eg, leukopenia and/or neutropenia) is not permitted.

Table 6 VGCV Dosage Recommendations for Adult Participants Based on Creatinine Clearance

CrCl* (mL/min)	**VGCV (450 mg Tablets) Dose**
≥60	900 mg (2 tablets) once daily
40 – 59	450 mg (1 tablet) once daily
25 – 39	450 mg (1 tablet) every 2 days
10 – 24	450 mg (1 tablet) twice weekly

Participants will need to maintain CrCl >10 mL/min throughout the treatment period with study medication.

*An estimated CrCl is calculated from serum creatinine by the following formula:

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

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

CrCl = creatinine clearance; VGCV = valganciclovir

[U.S. Prescribing Information 2017]

Table 7 GCV (Intravenous) Dosage Recommendations for Adult Participants Based on Creatinine Clearance

CrCl* (mL/min)	GCV for Injection Maintenance Dose (mg/kg)	Dosing Interval (hours)
≥70	5	24
50 – 69	2.5	24
25 – 49	1.25	24
10 – 24	0.625	24

Participants will need to maintain CrCl >10 mL/min throughout the treatment period with study medication.

*An estimated CrCl is calculated from serum creatinine by the following formula:

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

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

CrCl = creatinine clearance; GCV = ganciclovir

[U.S. Prescribing Information 2017]

Table 8 ACV (Oral) Dosage Recommendations for Adult Participants Based on Creatinine Clearance

CrCl* (mL/min)	ACV (400 mg Capsule or 400 mg Tablet) Dose
≥30	400 mg every 12 hours
>10 and <30	400 mg once daily

Participants will need to maintain CrCl >10 mL/min throughout the treatment period with study medication.

*An estimated CrCl is calculated from serum creatinine by the following formula:

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

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

ACV= acyclovir; CrCl = creatinine clearance

[Winston, D.J., et al 2012] [Zuckerman, R. A. 2013] [Gold, D. 1987]

Table 9 ACV (Intravenous) Dosage Recommendations for Adult Participants Based on Creatinine Clearance

CrCl* (mL/min)	ACV Dosing Regimen†
≥30	250 mg/m^2 every 12 hours
>10 and <30	250 mg/m^2 once daily

Participants will need to maintain CrCl >10 mL/min throughout the treatment period with study medication.

*An estimated CrCl is calculated from serum creatinine by the following formula:

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

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

ACV = acyclovir; BSA= body surface area; CrCl = creatinine clearance

[Tomblyn, M, et al 2009] [Gold, D. 1987]

†Total BSA (m^2) is calculated by the following (Mosteller) formula:

$$\text{Mosteller BSA}\,(m^2) = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to either the LET or VGCV treatment arm. Participants randomized to the LET arm and who require intravenous (IV) formulation of LET and who are not on concomitant CsA will undergo another randomization (1:1 centrally using IVRS/IWRS) to receive either 240mg IV LET QD or 480mg IV LET QD. See Sections 5.1 and 9.11.2.2 for additional details on LET dosing.

7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

- Use or non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction

Note: Such highly cytolytic, anti-lymphocyte immunotherapy includes the use of one or more of the following: horse-derived or rabbit-derived anti-thymocyte globulin, alemtuzumab (CAMPATH™), or muromonab-CD3 (OKT3). During the course of the study, this list may be expanded to include other anti-lymphocyte agents that are approved for induction therapy in kidney transplant recipients.

7.4 Blinding

A double-blinding technique with in-house blinding will be used. The oral formulations will be packaged identically so that treatment blind/masking is maintained. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.

Placebo images to LET (both 240 mg and 480 mg), VGCV, and ACV will be implemented to maintain study blinding, and placebo will be indistinguishable from these respective study therapies. Assuming normal renal function (Section 7.2), a participant randomized to the LET treatment arm will receive the following from Day 1 through Week 28:

- LET (one 480 mg tablet [or 2 × 240 mg tablets] or one 240 mg tablet if given concomitantly with CsA per day, ie, once daily)
- Placebo to VGCV (2 VGCV-matching placebo tablets per day, ie, once daily)
- ACV (two 400 mg capsules or tablets per day, ie, 1 capsule or tablet every 12 hours)

Accordingly, assuming normal renal function, a participant randomized to the VGCV treatment arm will receive the following from Day 1 through Week 28:

1. VGCV (two 450 mg tablets per day, ie, once daily)
2. Placebo to LET (one 480 mg LET-matching placebo tablet [or 2 × 240 mg LET-matching placebo tablets] or one 240 mg LET-matching placebo tablet if given concomitantly with CsA per day, ie, once daily)
3. Placebo to ACV (2 ACV-matching placebo capsules or tablets per day, ie, 1 capsule or tablet every 12 hours)

Table 10 summarizes use of oral study medication (active and placebo) for the LET and VGCV treatment arms by use of concomitant CsA for participants with normal renal function.

Table 10 Blinding of Oral Formulation Related to Concomitant CsA Use for Participants With Normal Renal Function

	LET Arm	VGCV Arm
With Concomitant CsA	• One 240 mg LET tablet • Two VGCV-matching placebo tablets • Two ACV 400 mg capsules or tablets (each capsule or tablet given every 12 hours)	• One 240 mg LET matching placebo tablet • Two VGCV 450 mg tablets • Two ACV-matching placebo capsules or tablets (each capsule or tablet given every 12 hours)
Without Concomitant CsA	• One 480 mg LET tablet or two 240 mg LET tablets • Two VGCV-matching placebo tablets • Two ACV 400 mg capsules or tablets (each capsule or tablet given every 12 hours)	• One 480 mg LET-matching placebo tablet or two 240 mg LET-matching placebo tablets • Two VGCV 450 mg tablets • Two ACV-matching placebo capsules or tablets (each capsule or tablet given every 12 hours)

ACV = acyclovir; CsA = cyclosporin A; LET = letermovir; VGCV = valganciclovir
Dose of VGCV and ACV will be modified based on creatinine clearance, see Section 7.2.

IV LET, IV GCV, IV ACV (for participants in the LET arm), and IV ACV matching placebo (for participants in the VGCV arm) will be prepared in a blinded fashion by an unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV study therapy). The Sponsor will provide opaque covers for the IV bags in order to assist with blinding IV study therapy.

Because this is a double-blind study, the investigator, study personnel, and participant must remain blinded to the IV study therapy (LET and ACV for participants in the LET arm and LET dose for those not on CsA [240 or 480 mg]; GCV and ACV matching placebo for participants in the VGCV arm). In order to maintain the blinding, the unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV study therapy) will be responsible solely for the preparation of the IV study therapy. He/she will not be involved in evaluating participants for efficacy or safety. The IV study therapy will be administered by blinded personnel of the site. Refer to the Pharmacy Manual for further details.

Table 11 summarizes use of IV study medication (active and placebo) for the LET and VGCV treatment arms by use of concomitant CsA for participants based on renal function.

Table 11 Blinding of IV Study Medication Related to Concomitant CsA Use for Participants Based on Renal Function

	LET Arm	VGCV Arm
With Concomitant CsA	CrCl ≥30 mL/min: • One 250-mL IV bag containing 240 mg LET (must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free) • Two 250-mL IV bags, each containing ACV 250 mg/m^2 × BSA (each bag given every 12 hours)[*] .	CrCl ≥30 mL/min: • One 250-mL IV bag containing GCV (see Table 7 for GCV dosage recommendations based on renal function) • Two 250-mL IV bags: ACV-matching placebo (each bag given every 12 hours); one of the ACV-matching placebo doses, ie, the one to be paired with IV GCV infusion, must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free
	CrCl >10 mL/min and <30 mL/min: • One 250-mL IV bag containing 240 mg LET (must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free) • One 250-mL IV bag containing ACV 250 mg/m^2 × BSA	CrCl >10 mL/min and <30 mL/min: • One 250-mL IV bag containing GCV (see Table 7 for GCV dosage recommendations based on renal function) • One 250-mL IV bag ACV-matching placebo to be paired with IV GCV infusion (must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free)

	LET Arm	VGCV Arm
Without Concomitant CsA	CrCl ≥30 mL/min: • One 250-mL IV bag containing 480 mg LET or 240 mg LET (must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free) • Two 250-mL IV bags, each containing ACV 250 mg/m^2 × BSA (each bag given every 12 hours)	CrCl ≥30 mL/min: • One 250-mL IV bag containing GCV (see Table 7 for GCV dosage recommendations based on renal function) • Two 250-mL IV bags: ACV-matching placebo (each bag given every 12 hours); one of the ACV-matching placebo doses, ie, the one to be paired with IV GCV infusion, must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free
	CrCl >10 mL/min and <30 mL/min: • One 250-mL IV bag containing 240 mg LET (must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free) • One 250-mL IV bag containing ACV 250 mg/m^2 × BSA	CrCl >10 mL/min and <30 mL/min: • One 250-mL IV bag containing GCV (see Table 7 for GCV dosage recommendations based on renal function) • One 250 mL IV bag: ACV-matching placebo to be paired with IV GCV infusion (must be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free)
ACV = acyclovir; BSA= body surface area; CsA = cyclosporin A; GCV = ganciclovir; IV = intravenous; LET = letermovir; VGCV = valganciclovir Dose of GCV and ACV will be modified based on creatinine clearance, see Section 7.2. *The maximum concentration of ACV for IV infusion is not to exceed 7 mg/mL as specified per the product label.		

If a participant's dose of VGCV or VGCV matching placebo is modified due to renal insufficiency (see Section 7.2), the blinding to VGCV or VGCV matching placebo will be maintained. Similarly, if a participant's dose of ACV or ACV matching placebo is modified due to renal insufficiency (see Section 7.2), the blinding to ACV or ACV matching placebo will be maintained.

See Section 9.1.11 for a description of the method of unblinding a participant during the trial, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

For the oral formulation, participants will receive blinded bottles (each containing a 2-week supply of study therapy). Kitting will not be used, and participants will be provided bottles of study drug representing the appropriate drug types used in the study per each treatment cycle.

For the IV formulation, open-label vials of LET, ACV and GCV will be supplied to the sites. The IV formulation will be dispensed in a blinded fashion by an unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV therapy) as directed by the protocol to the appropriate dosage for each participant.

The LET IV formulation dosing volume will be 250 mL and the duration of infusion will be 60 minutes. LET IV will be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter using IV bags and infusion set materials that are DEHP-free.

To reduce the risk of unblinding, the same administration instructions for LET IV will apply to the dose of IV placebo to ACV that is paired with the dosing of GCV IV (Table 11).

To further reduce the risk of unblinding, the infusion volume of GCV IV formulation will be 250 mL and it will be dosed at 5 mg/kg body weight (see Table 7 for GCV dosing adjustment based on CrCl) and the duration of infusion will be 60 minutes.

The ACV IV formulation will be 250 mL and dosed at 250 mg/m^2 (see Table 9 for ACV dosing adjustment based on CrCl) BSA and the duration of infusion will be 60 minutes. The maximum concentration of ACV for IV infusion is not to exceed 7 mg/mL, as specified per the product label.

7.5.2 Handling, Storage and Accountability

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

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial 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 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.

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 treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

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

If oral medication is administered by clinical personnel during any hospitalization or comparable inpatient setting (including but not limited to skilled nursing facility or rehabilitation facility) in which non-study and study medications are administered by clinical personnel), 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 by blinded personnel. The investigator/study coordinator will be responsible for transferring the appropriate information to the case report form.

Study therapy (ie, all three oral study medications or both IV study medications) may be interrupted for any reason for a time period of ≤7 consecutive days (including suspected CMV Disease; see Section 9.2.1); in such cases, all study therapy (ie, all three oral study medications or both IV study medications) should be interrupted. Interruption of a subset of study therapy (eg, one or two out of three oral study medications or one out of two IV study medications) will not be permitted (except in the event of HSV/VZV infection, see Section 7.7.1). Study therapy interruption due to post-randomization CrCl ≤10 mL/min or requirement for dialysis or plasmapheresis is described in Section 9.1.9.1. Interruption from the protocol specified treatment for a time period of ≤7 consecutive days due to an AE followed by re-starting of protocol specified treatment 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.

7.7 Concomitant Therapy

Medications/therapies listed in this section pertain to co-administration with LET, VGCV, and ACV. When used, these agents should be administered in a manner consistent with the local product circular for these agents (if available for LET) including the complete list of prohibited medications (ie, those that are contraindicated or not recommended); the local product circular for these agents (if available for LET) supersedes Section 7.7 with respect to prohibited medications. Additional information on LET use is provided in the IB.

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 medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy 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 therapy 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.

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

Prohibited Medication

Listed below are specific restrictions for concomitant therapy during the course of the trial.

- 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 for co-administered medication for drug interactions with CsA).

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

- Certain HMG-CoA reductase inhibitors (statins): When LET is co-administered with CsA, the magnitude of the increase in statin plasma concentrations is expected to be greater than with LET alone.
    - Simvastatin or pitavastatin with LET or when LET is co-administered with CsA.
    - Atorvastatin or lovastatin when LET is co-administered with CsA.
        - Note: see below for co-administration of LET with atorvastatin, fluvastatin, lovastatin, rosuvastatin, or pravastatin.
- Fixed dose combination products containing statins are not allowed because the dosage of statins should be adjusted when LET is co-administered.
- Strong inducers, such as rifampin, phenytoin, carbamazepine, St John's wort (Hypericum perforatum), rifabutin and phenobarbital
- Moderate inducers, such as nafcillin, thioridazine, modafinil and bosentan
- Cytochrome P450 3A (CYP3A) substrates with narrow therapeutic range (NTR) that can lead to SAEs, including but not limited to:
    - Pimozide: Concomitant administration of LET may result in increased concentrations of pimozide due to inhibition of CYP3A by LET, which may lead to QT prolongation and torsade de pointes.
    - Ergot alkaloids: Concomitant administration of LET may result in increased concentration of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by LET, which may lead to ergotism.
- Repaglinide when LET is co-administered with CsA (Note: see below for co-administration of LET with repaglinide).
- Everolimus when LET is co-administered with CsA (Note: see below for co-administration of LET with everolimus).
- Any investigational CMV antiviral agent/biologic therapy, including CMV vaccines or CMV hyper-immune globulin except for GCV or VGCV as used as study medication in this trial.
- The following medications/therapies are prohibited for the prevention/treatment of CMV while participants are on study therapy (except for cases of suspected CMV Disease; see Section 9.2.1). Participants for whom cidofovir or foscarnet is administered for non-CMV infections (eg, cidofovir for treatment of BK virus

infection) must interrupt all study medications during cidofovir or foscarnet administration (see Section 7.6 regarding the duration of interruption of study medications). ACV, valacyclovir, and famciclovir may be used at thresholds lower than specified below (for a subset of these medications for which such thresholds are specified):

- LET that is not part of study intervention
- GCV or VGCV that is not part of study intervention
- Foscarnet (see above)
- Cidofovir (see above)
- ACV (at doses >3200 mg PO per day or >25 mg/kg IV per day)
- Valacyclovir (at doses >3000 mg or ≤500 mg PO per day, and not for HSV/VZV prophylaxis; see below)
- Famciclovir (at doses >1500 mg or ≤1000 mg PO per day, and not for HSV/VZV prophylaxis; see below)
- Note: The use of oral ACV at doses stated in this protocol is allowed for prophylaxis of HSV or VZV infections at lower doses as per manufacturer's recommendation. The use of valacyclovir or famciclovir for HSV/VZV prophylaxis is not permitted in this trial. The use of ACV, valacyclovir, or famciclovir for HSV/VZV infections (herpes labialis, herpes zoster, or genital herpes) within the dose ranges specified is permitted; during such instances, the use of ACV versus matching placebo should be stopped (see Section 7.7.1).

- Imipenem-cilastatin
- Investigational Agents: Unapproved investigational agents or investigational regimens involving combinations of *approved* agents (eg, immunosuppressive agents) are not permitted.
- Herbal Supplements: Herbal supplements are not permitted.

The following medications/therapies may require dose adjustment or closer monitoring during the dosing period and for 14 days after the dosing period:

- Inhibitors of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters:
  - CsA: Co-administration of LET with CsA, a potent OATP1B1/3 inhibitor, increases the concentrations of LET. If LET is co-administered with CsA, the recommended dose of LET is 240 mg once daily.

- Substrates of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) and/or CYP3A:
    - Statins:
        - Atorvastatin: The dose of atorvastatin should not exceed a daily dose of 20 mg. Atorvastatin is prohibited when co-administered with LET and CsA (see above).
        - Fluvastatin, lovastatin, rosuvastatin, or pravastatin: The dose of fluvastatin, lovastatin, rosuvastatin, or pravastatin may need to be adjusted when co-administered with LET. Lovastatin is prohibited when co-administered with LET and CsA (see above). Monitoring for statin-associated adverse reactions (eg, myalgias, rhabdomyolysis) is recommended during co-administration.
    - Glyburide, a substrate of OATP1B1/3: Frequent monitoring of glucose concentrations is recommended during co administration of glyburide with LET.
- Substrates of CYP2C8 (repaglinide, rosiglitazone):
    - Repaglinide, rosiglitazone: LET is an in vitro inhibitor of CYP2C8. Co-administration of LET with CYP2C8 substrates (eg, repaglinide, rosiglitazone) may increase the plasma concentrations of CYP2C8 substrates. Frequent monitoring of glucose concentrations is recommended during co-administration of repaglinide and rosiglitazone and LET.
- 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 (examples: alfentanil, fentanyl, midazolam, quinidine). Therefore, frequent monitoring for adverse reactions related to these agents is recommended during co-administration. When LET is co-administered with CsA, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the prescribing information for CsA and for co-administered medication for dosing of the CYP3A substrate with a strong CYP3A inhibitor.
    - 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 accordingly.

- 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 accordingly.

  When LET is co-administered with CsA, refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with CsA.

- 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 accordingly.

- 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 above).

- Amiodarone: LET may increase the plasma concentrations of amiodarone (CYP3A and CYP2C8 substrates). Frequent monitoring for adverse reactions related amiodarone is recommended during co-administration. Frequent monitoring of amiodarone concentrations should be performed when co-administered with LET.

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

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

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

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

Concomitant Use with VGCV/GCV

Note: In vivo drug-drug interaction studies were not conducted with VGCV. However, because VGCV is rapidly and extensively converted to GCV, drug-drug interactions associated with GCV will be expected for VGCV. Drug-drug interaction studies with GCV were conducted in patients with normal renal function. Following concomitant administration of VGCV and other renally excreted drugs, patients with impaired renal function may have increased concentrations of GCV and the co-administered drug. Therefore, these patients should be closely monitored for toxicity of GCV and the co-administered drug [U.S. Prescribing Information 2017].

Potential drug interactions may occur when the following drugs are co-administered with VGCV/GCV and should therefore be closely monitored as described below:

- CsA or amphotericin B: Monitor renal function because of potential increase in serum creatinine.
- Probenecid: May increase GCV levels. Monitor for evidence of GCV toxicity (eg, neutropenia).
- MMF: In patients with renal impairment GCV concentrations and MMF metabolite concentrations may increase. Monitor for GCV (eg, neutropenia) and MMF toxicity (eg, neutropenia, red-cell aplasia, viral infections, and/or lymphoproliferative disorders).
- Didanosine: Patients should be closely monitored for didanosine toxicity (eg, pancreatitis).
- Other drugs associated with myelosuppression or nephrotoxicity (eg, adriamycin, dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, trimethoprim/sulfamethoxazole, vinblastine, vincristine, and zidovudine): Because of potential for higher toxicity, co-administration with VGCV/GCV should be considered only if the potential benefits are judged to outweigh the risks [U.S. Prescribing Information 2017].

Note: Please also see Section 6.3.1 for dietary restrictions.

Concomitant Use with ACV

Potential drug interactions with probenecid may occur when it is co-administered with intravenous ACV as co-administration of probenecid with ACV IV has been shown to increase the mean ACV half-life and the area under the concentration-time curve. Dose adjustment may be required for ACV IV when co-administered with probenecid.

Concomitant medications and therapies that are discontinued or dose adjusted during the dosing period may be restarted or re-adjusted 2 weeks after the last dose of study drug is administered and may continue during the follow-up period.

NOTE: For other medications not listed here, please consult with the Sponsor as needed.

7.7.1 Rescue Medications & 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 start CMV treatment due to any other reason, study therapy will be discontinued (see Section 9.2.1) 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 7.7) can be used.

In the event of HSV/VZV infection (as diagnosed by the investigator; herpes labialis, herpes zoster, and genital herpes) during the study therapy period (ie, prior to completion or early discontinuation of study therapy), the ACV study medication will be interrupted and the participant may be treated according to the local SOC (outside the context of the study) while continuing other study medications (LET + VGCV matching placebo versus VGCV + LET matching placebo). In this setting, valacyclovir or famciclovir or ACV at dose ranges outlined in Section 7.7 can be used.

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind participants and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 9.1.11). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.11, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period

will still continue to participate in the study as specified in Section 2 - Schedule of Activities and Section 9.11.4 – CMV Disease or Early Discontinuation Visit.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.10 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment 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 treatment.
- The participant develops confirmed or suspected CMV disease as determined by the investigator (Section 5.4.1.1).
- 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:
    - Both moderate hepatic insufficiency (Child-Pugh Class B; Appendix 8) and moderate-to-severe renal insufficiency (defined as CrCl <50 mL/min as calculated by the Cockcroft-Gault equation; see Section 6.2),

      OR

    - Severe hepatic insufficiency (Child-Pugh Class C; Appendix 8).

The participant **may** be discontinued from study therapy for any of the following reasons:

- Any AE/SAE assessed by the investigator as possibly or probably related to study therapy. The investigator may continue the participant in the study if it is deemed to be in the best interest of the participant to stay on study therapy.
- Failure to comply with the dosing, evaluations, or other requirements of the study.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk through continued participation in the study or does not allow the participant to adhere to the requirements of the protocol (eg, if there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required [see Section 7.7]).

Participants who interrupt (see Section 9.2.1) or discontinue study therapy prior to Week 28 because they are suspected of developing CMV disease must complete a CMV Disease Visit (Sections 2 (SoA) and 9.11.4.1). A CMV Disease Visit may be performed at any time when one or more criteria for the CMV Disease Visit (Section 9.11.4.1) is fulfilled. If the participant presents with signs/symptoms of CMV disease at a scheduled study visit, then the procedures for a CMV Disease 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 2), are performed at the CMV Disease Visit **immediately prior to** the initiation of treatment of CMV disease. Most importantly, a confirmatory plasma sample for CMV DNA PCR testing, a plasma sample for CMV viral resistance testing (note: once the CMV Disease visit occurs, another plasma sample for CMV viral resistance testing should be collected at the next scheduled visit; see Sections 9.5.8.2 and 9.5.8.3), 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 2). 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.

Participants with confirmed CMV disease at any time during the study will complete all remaining scheduled visits (ie, through Week 52).

For participants who are discontinued from study treatment but continue to be monitored in the trial, see Section 2 – Schedule of Activities (SoA), and Section 9.11.4 – CMV Disease or Early Discontinuation Visit for those procedures to be completed at each specified visit.

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

8.2 Withdrawal from the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from Future Biomedical Research, are outlined in Section 9.1.10 – Withdrawal/Discontinuation. 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 8.3.

8.3 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, phone 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 amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9. 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 assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of trial site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- 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 subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The amount of blood collected from each participant over the duration of the study is provided in Table 18.

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

9.1 Administrative and General Procedures

9.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial, or Future Biomedical Research, or optional PK collection at Week 1 (applicable for non-Asian participants). If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

9.1.1.1 General Informed Consent

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

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

The initial ICF, any subsequent revised written 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 trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

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

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the participant.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study at screening and on Day 1 (randomization).

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent. At the time of treatment 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 health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

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

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement. This includes review of consumption of grapefruit, Seville oranges or their respective juices, and other quinine-containing drinks or food. Prior medication taken by the participant within 30 days prior to randomization will be recorded.

9.1.5.2 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 therapy 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, antiparasitic agents, and antivirals), oral hypoglycemic agents, insulin, granulocyte colony-stimulating factor (G-CSF), and immunosuppressant agents.

9.1.6 Kidney Transplant/Dialysis Details Review

All relevant data about the kidney transplant will be collected on Day 1 (at randomization). 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.

9.1.7 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 randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Those participants who meet any of the laboratory exclusion criteria in Table 3 at screening and whose planned/scheduled kidney transplant was not performed may be rescreened for study eligibility. To reconfirm the participant's eligibility, all screening evaluations should be repeated, after approval from the Sponsor. Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.11.1.

9.1.8 Assignment of Treatment/Randomization Number

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

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

9.1.9 Treatment Administration

The first dose of study treatment will be administered at the trial site on Day 1 after randomization. Subsequent oral dosing will be performed by the participant (eg, self-administered at his/her home). See Section 7.6 for details regarding oral medication administered during any hospitalization or comparable inpatient setting (including but not

limited to skilled nursing facility or rehabilitation facility). For IV formulation, the unblinded pharmacist (or qualified study site personnel designated to prepare blinded IV study therapy) will be responsible solely for the preparation of the IV study therapy. The IV study therapy will be administered by blinded site personnel. IV LET and, where appropriate, placebo to IV ACV will be administered through a sterile 0.2-micron or 0.22-micron PES in-line filter and using DEHP-free IV bags and infusion set materials. Refer to the Pharmacy Manual for further details.

9.1.9.1 Timing of Dose Administration

Study therapy should be taken at approximately the same time each day for the duration of the study (ie, once daily for LET or VGCV; every 12 hours for ACV). Tablets or capsules are to be swallowed whole (ie, no crushing or chewing is allowed). Since VGCV tablets are recommended to be taken with food, study therapy in all treatment arms should be taken with food. Treatment compliance is further described in Section 7.6.

If a participant misses a dose of study medication, the missed dose should be taken as soon as possible during the same day. Then, the next dose should be taken at the normally scheduled time. However, if more than 18 hours have elapsed 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.

Participants with post-randomization CrCl ≤10 mL/min or who require dialysis or plasmapheresis after randomization will have all of 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.

9.1.10 Withdrawal/Discontinuation

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

When a participant withdraws from participation in the trial, all applicable activities scheduled for the Early Discontinuation Visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for Future Biomedical Research 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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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.

9.1.11 Participant Blinding/Unblinding

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

For emergency situations where the investigator or delegate needs to identify the drug used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator or delegate must enter the intensity of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for participant safety.

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the participant. Every effort should be made not to unblind the participant unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

9.1.12 Domiciling

For participants who will undergo intensive PK sampling, the investigator should make arrangements (including local accommodations outside the context of hospitalization, if needed/warranted) 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.

9.1.13 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.

Volumetric pump (not provided by the Sponsor)

9.2 Efficacy Assessments

9.2.1 CMV Disease Assessment

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 7. If CMV Disease is suspected, site should perform the CMV Disease Visit instead of the scheduled visit assessments (see Sections 2 (SoA) and 9.11.4.1) 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 7 will be collected.

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

Note: It is mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory **immediately prior to** (ie, on the day of) initiating treatment for confirmed or suspected CMV disease. In the event that the confirmatory result obtained on the day of anti-CMV treatment initiation is **NOT** available (eg, sample is lost or mishandled by the investigator site prior to shipment, or is inadequate upon receipt at the central laboratory), a subsequent sample must be obtained and sent to the central laboratory within 7 days after initiation of anti-CMV treatment (preferably within 48-72 hours).

If CMV disease is confirmed by the investigator while the participant is on study treatment or a clinical decision is made by the investigator to stop study medication and start CMV treatment due to any other reason (eg, symptomatic CMV DNAemia without meeting the criteria for CMV syndrome): The participant's study therapy will be discontinued (see following bullet) and a CMV Disease Visit (including collection of CMV DNA PCR and a CMV viral resistance sample; see Section 2 (SoA)) will be completed prior to initiating

standard-of-care treatment for CMV disease, which may be started at the investigator's discretion [Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S 2013]. 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 SoA (Section 2). 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.

- Following the CMV Disease Visit, a participant may interrupt study treatment (if the participant is on study treatment at the time of the CMV Disease Visit) and receive standard-of-care treatment for CMV Disease 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 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 standard-of-care treatment for CMV Disease and resume previously assigned study treatment.

If CMV disease is suspected or confirmed by the investigator during the post-treatment follow-up period (ie, after completion or early discontinuation of study therapy): Participants may be started on standard-of-care treatment for CMV disease at the investigator's discretion and will complete all remaining follow-up visits (through Week 52; Section 2). See Section 2 (SoA) for procedures performed at the CMV Disease Visit.

9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (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 4.

AE, 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, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

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

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

From the time of treatment allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs and other reportable safety events must be reported by the investigator.

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 to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment 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 timeframes as indicated in Table 12 .

Table 12 Reporting Time Periods and Timeframes 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		Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - subject 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 - subject 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

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		Timeframe to Report Event and Follow-up Information to SPONSOR:
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 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

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events

including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 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 treatment 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 treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

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

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

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints (Health Outcomes) including re-hospitalizations (including re-hospitalizations 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 9.10.1 for a complete list) must be collected throughout the study (ie, during both treatment and follow-up). From the time of treatment allocation/randomization, through 14 days following cessation of treatment, these events must be reported as described in Section 9.3.1. 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 adverse events if they are assessed as serious and there is evidence to suggest a causal relationship between the drug and the adverse event. An external Data Monitoring Committee (DMC) will monitor the interim data from this trial (see Appendix 3).

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously

reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the trial 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.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. 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 trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

9.4 Treatment of Overdose

In this study, an overdose is any dose higher than two times the prescribed dose specified in Section 7.2 (Dose Modification [Escalation/Titration/Other]). Overdose during the study will be a reportable safety event (see Section 9.3.1 and Appendix 4 for further details).

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from screening through Week 52), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in Appendix 2, Table 18.

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

9.5.1 Physical Examinations

All physical examinations must be performed by the principal investigator or subinvestigator (physician, physician assistant, or nurse practitioner).

A complete physical examination, performed at the screening visit, Day 1 (randomization), and Week 28, includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic examinations should be performed when clinically indicated.

After randomization (Day 1), 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 2).

9.5.2 Weight and Height Assessment

The participant's weight and height will be assessed as indicated in the Study SoA (Section 2).

9.5.3 Vital Signs

Vital signs will be assessed as indicated in the Study SoA (Section 2).

Vital signs will include heart rate (sitting), blood pressure (sitting), respiratory rate, and body temperature (oral preferred; see below). Participants should be resting for at least 10 minutes prior to measurement of vital signs.

Note: Temperatures should be taken orally, but if oral is not possible, tympanic, rectal, and axillary temperatures are acceptable.

9.5.4 12-Lead Electrocardiogram

As indicated in the SoA (Section 2), 12-Lead ECG measurements will be performed and read locally. If participants have had ECG measurements collected within 3 months prior to screening and if such prior ECG measurements are available for the study, ECG measurements will not need to be obtained at screening.

Participants should be shaved as necessary for proper lead placement. Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained.

9.5.5 Child-Pugh Score

The Child-Pugh Score will be assessed as indicated in the Study SoA (Section 2) according to Appendix 8. At the screening visit, the clinical assessment and the local 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 8.1, 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 6.2), or develops severe hepatic insufficiency (Child-Pugh Class C).

9.5.6 Birth Control Confirmation

Participants must use acceptable methods of contraception from the time of consent through 90 days after the last dose of study therapy (see Appendix 5). Confirmation must be obtained by site personnel that participants and their partner(s) are using acceptable methods of contraception. This assessment must be documented in the participant's study chart at each specified visit.

9.5.7 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 9.3 (Assessing and Recording Adverse Events) for further details.

Infusion-Site Adverse Events for Participants Administered IV Study Therapy

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 therapy. Events will be entered on the AEs electronic case report form. The study site guidance for assessment and follow-up for infusion-site AEs can be found in the Investigator Trial File Binder.

9.5.8 Clinical Safety Laboratory Assessments

9.5.8.1 Laboratory Safety Evaluations

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

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

- If laboratory values from non-protocol 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 treatment, 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.

9.5.8.2 CMV DNA PCR Testing

Protocol-specified CMV DNA levels will be drawn at prespecified clinical visits: at randomization, 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 2).

In this study, the monitoring of CMV DNA levels for the clinical management of participants will be performed locally, ie, "for cause" CMV DNA levels may be measured at any time during the study at the discretion of the site investigator and/or clinical management team. When a CMV DNA PCR is drawn at the site and sent to a local laboratory for clinical management of a participant, it is mandatory that a separate blood sample also be collected for CMV DNA PCR and sent to the central laboratory for processing. There is no protocol-specified threshold for diagnosis of CMV disease and/or stopping CMV prophylaxis and initiating CMV disease therapy. "For cause" CMV DNA levels will be available to the site investigator.

At the CMV Disease Visit, a blood sample will be taken for a CMV DNA PCR assessment (see note below).

Note: It is mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory **immediately prior to** (ie, on the day of) initiating treatment for confirmed or suspected CMV disease. In the event that the confirmatory result obtained on the day of anti-CMV treatment initiation is **NOT** available (eg, sample is lost or mishandled by the investigator site prior to shipment, or is inadequate upon receipt at the central laboratory), a subsequent sample must be obtained and sent to the central laboratory within 7 days after initiation of anti-CMV treatment (preferably within 48-72 hours).

Central laboratory based CMV DNA levels (as well as "for cause" assessments; see above) will be retrospectively analyzed at the end of the study. The central laboratory based CMV DNA levels will not be shared with the respective site investigators.

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

9.5.8.3 CMV Viral Resistance Testing

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

CMV 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 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 Disease visit 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 CMV treatment; or (3) -initiation of CMV treatment during the follow-up period (see Section 2). Once the CMV Disease 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 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.

9.5.8.4 CMV UL55 (gB) Genotypic Testing

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

The CMV glycoprotein B (gB) genotype will be determined by DNA sequencing of the CMV UL55 gene in plasma samples collected from participants who meet the criteria for confirmed CMV disease or in whom study therapy was stopped and CMV treatment was started. Five different gB genotypes (gB1/gB2/gB3/gB4/gB5) have been described for CMV clinical isolates, with a defined DNA sequence of the UL55 gene that is associated with each gB genotype. To perform the gB genotyping, a portion of the UL55 gene will be amplified by PCR from total DNA isolated from plasma, and the DNA sequence of the PCR products will be determined by next-generation sequencing. The genotyping procedure will be performed by an established contract laboratory with validated protocols in place.

The CMV gB genotyping report will identify any genotype(s) that were detected in each sample evaluated; for samples with more than one genotype detected, the relative abundance of each genotype will be reported.

9.5.8.5 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 180 days of randomization 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.

9.6 Pharmacokinetics

9.6.1 Blood Collection for Plasma Letermovir

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

Population (sparse) PK samples 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.

The intensive PK samples will be collected at the Week 1 visit for participants (ie, of Asian descent, and consenting participants of non-Asian descent; see Sections 2 and 5.4.1.4 for further details) who receive oral or IV formulation of study medication at the following timepoints:

- 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)
- 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)

The intensive PK samples will be collected for all participants who have received >5 consecutive days of IV administration – no more than ONCE during the entire study, regardless of how many times the IV therapy criterion is fulfilled during the study (see Sections 2 and 5.4.1.4 for further details). The timing of the intensive PK collection will be after 5 days of consecutive administration of IV treatment (ie, 6th consecutive day of IV treatment) at the following timepoints prior to and after start of study medication infusion:

- Pre-dose (within 0-2 hours prior to dose)
- 1 hour (within 10 min **after** infusion completion)

- 2.5 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)

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- 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.

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. Blood samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA.

9.9.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual. 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 Institutional Review Board (IRB)/Independent Ethics Committee (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 extract DNA will be stored for future biomedical research if the participant signs the Future Biomedical Research consent.

9.10 Health Outcomes and Quality of Life Assessments

9.10.1 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 2). Select

OIs [Kidney Disease: Improving Global Outcomes Transplant Work Group 2009] [Trofe-Clark, J. 2016] are as follows:

- *Pneumocystis jirovecii* pneumonia (PJP)
- 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

9.10.2 Quality of Life Assessments

Quality of life (QoL) will be assessed using two electronic instruments, the EQ-5D and the SF-36v2® Health Survey. Questionnaires will be administered as described in the Study SoA (Section 2). The two questionnaires will be completed at the beginning of study visit (ie, before any other procedures are performed). There will be no specific order for EQ-5D and SF-36v2® administration.

The EQ-5D measures Health-related (HR) QoL on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a 20-cm vertical visual analog scale (VAS) that generates a self-rating of HRQoL. The EQ-5D has shown acceptable construct and concurrent validity in kidney transplant and is a valid instrument for measurement of health status in renal transplant patients [Cleemput, I., et al 2004].

The SF-36v2® Health Survey, Standard (4-week recall) Form, is a generic health survey which includes 36 questions to measure functional health and well-being from the participant's perspective. The standard, 4-week recall version of the form was selected to detect overall changes in health status. The SF-36v2® measures each of the following eight health domains: Physical Functioning, Role Limitations-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations-Emotional, and Mental Health. The 8 health domain scores contribute to the computation of the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores [Barotfi, S., et al 2006].

9.11 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.11.1 Screening

Screening of potentially eligible participants may begin on the day of transplantation (ie, prior to transplantation) or 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. Participants will be randomized 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 9.5.7.

Potential participants will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as described in Sections 6.1 and 6.2. 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 2) will be performed and must be completed by Day 5 post-transplant (inclusive). Participants will be instructed that they are required to use birth control, as described in Appendix 5, starting from the time of consent through 90 days after the last dose of study therapy (or longer if dictated by local regulations). Participants will also be instructed about the restrictions for concomitant medications, as noted in Section 7.7.

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 Table 17). Laboratory values may be collected centrally with the exception of CrCl measurements performed locally prior to randomization (see Exclusion Criterion #6 in Section 6.2) as well as any other local laboratory measurements for participant management outside the context of the protocol.

Human immunodeficiency virus (HIV) antibody test results documented at any time prior to randomization of the participant will be acceptable; a copy of this HIV report must be available. (See Exclusion Criterion #10 in Section 6.2). 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 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).

On the day of randomization, eligibility for enrollment into the study should be confirmed. Participants will be considered eligible for randomization once (a) they are determined to

have a documented negative serostatus and (b) have acceptable CrCl and liver function test values (ie, within the range allowed in this study, as outlined in Section 6.2 [Exclusion Criteria]).

Presence of CMV disease in the screening period will be assessed according to Appendix 7.

Rescreening

Those participants who meet any of the laboratory exclusion criteria in Table 3 and/or Child-Pugh classification in Exclusion Criterion 8 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.

9.11.2 Treatment Period

Study therapy will begin within 7 days post-transplant and will continue through Week 28. The Day 1 Visit (as shown in the Study SoA, Section 2) will be the day the participant is randomized and study therapy 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 2). 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 2) for CMV viral 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 therapy. Note that serum creatinine screening intervals should occur according to the recommendations listed in the Kidney Disease Improves Global Outcomes (KDIGO) Clinical Practice Guidelines [Kidney Disease: Improving Global Outcomes Transplant Work Group 2009] as part of a participant's SOC post-kidney transplantation.

9.11.2.1 Day 1 Visit

Day 1 procedures/assessments listed in the Study SoA (Section 2) must be performed prior to initiation of study therapy. Assessments of QoLs (ie, EQ-5D and SF-36v2®) should be completed prior to any study procedures at this visit.

Laboratory safety evaluations (hematology, chemistry, urinalysis, and other) specified in Section 9.5.8.1 will be performed prior to study therapy initiation. These samples will be sent to the appropriate central laboratory (or laboratories) following the procedure(s) described in the manual(s).

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

A serum pregnancy test may be performed on Day 1 for those WOCBP participants who are anuric and/or unable to provide urine.

For male participants, serum Inhibin B, LH, follicle stimulating hormone (FSH), and testosterone testing will be performed.

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

The first dose of study therapy (LET + placebo to VGCV + ACV, or VGCV + placebo to LET + placebo to ACV) will be administered at the trial site with monitoring by investigative site personnel at the Day 1 Visit (note: after population PK sample collection on Day 1). For participants who cannot swallow and/or have a condition that may interfere with the absorption of the oral formulation at or after randomization/Day 1, study therapy can be initiated/switched to the IV formulation. Participants should be switched from the IV formulation back to oral study therapy as soon as such participants are able to swallow and/or the condition necessitating the use of the IV formulation resolves and the appropriate oral study drug supply may be obtained for the participant. Use of the IV formulation should generally be limited to 4 weeks or less in duration per participant. However, it will be left to the investigator's discretion to continue IV administration beyond 4 weeks, if the benefit/risk ratio supports continued administration.

Participants in the LET treatment arm who are not on CsA will receive LET 480 mg QD given orally (either as one 480 mg tablet or two 240 mg tablets, at the investigator's discretion based on participant's swallowing capability). Participants who were initiated with two tablets of the LET 240 mg or matching placebo should continue with that regimen. Participants in the LET treatment arm 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 be randomized 1:1 to receive either 240 mg QD of IV LET or 480 mg QD of IV LET (Section 5.1). Participants requiring the IV formulation of LET who are on concomitant CsA will receive 240 mg QD of IV LET.

If CsA is initiated after starting study therapy 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 therapy 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 initiated after starting study therapy at an IV dose of LET 240 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 maintained at 240 mg QD.

If CsA is discontinued during the study therapy period for more than 3 consecutive days, the dose of oral LET (next administered up to 24 hours later) should be increased from 240 mg to 480 mg QD. If CsA is discontinued during study therapy period for more than 3 consecutive days and the subject is receiving IV formulation of LET 240 mg QD, then the subject will undergo 1:1 randomization to receive either 240 mg QD or 480 mg QD of IV formulation of LET (Section 5.1). If CsA is temporarily withheld (ie, ≤3 consecutive days) due to high levels detected by therapeutic blood monitoring, the dose of LET need not be adjusted. Corresponding changes in tablets for oral formulation with changes in CsA dosing will also occur in the VGCV arm in an effort to maintain the study blind (Section 7.4).

For prophylaxis against HSV and VZV, all participants will receive either oral ACV 400 mg every 12 hours or matching placebo, depending on randomization into the LET or VGCV treatment arm, respectively. If participants assigned to receive ACV cannot swallow capsules or tablets during the study, then such participants can also receive IV ACV at 250 mg/m^2 every 12 hours. The HSV/VZV prophylaxis will continue to Week 28. After Week 28, locally sourced ACV can be continued on an open-label basis at the discretion of the investigator.

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

The participant will be trained in the use of the Study Medication Diary. Once the participant is discharged from the hospital, he/she will be instructed to enter the number of tablets or capsules of study therapy taken during the study therapy period. See Section 7.6 for details regarding oral medication administered during any hospitalization or comparable inpatient setting (including but not limited to skilled nursing facility or rehabilitation facility) and use of IV formulation.

9.11.3 Follow-up Period

After completion of study therapy at Week 28, participants will continue to be followed for efficacy and safety, 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, and (7) QoL measures using validated PRO tools.

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 2). All scheduled study visits will be completed regardless of when cessation of study treatment occurs.

During the follow-up period, samples for CMV DNA PCR should be sent to the **central laboratory** as per the Study SoA (Section 2).

9.11.4 CMV Disease or Early Discontinuation Visit

9.11.4.1 CMV Disease Visit

The CMV Disease 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 2 [SoA] and Section 9.2.1). It is very important to ensure that all procedures, as outlined in the Study SoA (Section 2), are performed at the CMV Disease Visit **immediately prior to** the initiation of treatment of CMV disease (ie, on the day anti-CMV therapy is initiated). Most importantly, a confirmatory plasma sample for CMV DNA PCR testing as well as a plasma sample for CMV viral resistance testing should be collected at this visit and sent to the central laboratory. Additionally, a repeat plasma sample for CMV viral resistance testing should be collected at the next scheduled visit after the CMV Disease Visit (Section 9.5.8.3).

After the CMV Disease Visit, participants 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 2). 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.

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 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 (preferably within 48-72 hours; Section 9.5.8.2).

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

9.11.4.2 Discontinuation for Reasons Other Than CMV Disease

Study Therapy Discontinuation

Participants who discontinue study therapy prior to the last scheduled treatment visit for reasons other than CMV disease 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 2). 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

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 2), 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.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan (SAP) and referenced in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the supplemental SAP) will be developed to detail other planned analyses (ie, those specific to the analysis of PK data, genetic data, and PROs).

10.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Section 10.2 to Section 10.12.

Study Design Overview	A Phase III, Randomized, Double-Blind, Comparator-controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients
Treatment Assignment	This is a double-blind study with a 1:1 randomization ratio. Treatment allocation / randomization will be stratified by use or non-use of highly cytolytic anti-lymphocyte immunotherapy during induction**.**
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint	Proportion of participants with adjudicated CMV disease through 52 weeks post-transplant
Key Secondary Endpoints	Proportion of participants with adjudicated CMV disease through 28 weeks post-transplant Time to onset of adjudicated CMV disease through 52 weeks post-transplant
Statistical Methods for Key Efficacy Analyses	For the primary hypothesis, LET will be considered non-inferior to VGCV if the upper bound of the two-sided 95% CI for the proportion of participants with adjudicated CMV disease for (LET minus VGCV) is no higher than 0.10 (non-inferiority margin).
Statistical Methods for Key Safety Analyses	For safety events, p-values (Tier 1 only) and 95% CIs (Tier 1 and Tier 2) for between-treatment differences in the percentage of participants with events will be calculated using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	No interim analyses are planned for this study.
Multiplicity	Superiority for the primary hypotheses will be tested only if non-inferiority is demonstrated. Due to the principles of closed testing, no adjustment for multiplicity is required for the superiority test.
Sample Size and Power	The planned sample size is 600. For the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant, the trial has 90% power to demonstrate that LET is non-inferior to VGCV at an overall two-sided 5% alpha-level.

10.2 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. Certain specific analyses such as those for PK, pharmacogenetics, and QoL measures will be the responsibility of the appropriate departments of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedules: both the initial randomization for study treatment assignment and the second allocation schedule

for IV dosing for those participants not on concomitant CsA. Randomization will be implemented in the IVRS.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.

10.4 Analysis Endpoints

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

10.4.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 5.4.1.1.

The primary efficacy endpoint will be the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant. If the primary objective of non-inferiority is achieved, superiority of LET versus VGCV will be evaluated by comparing the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant.

CMV disease is defined as the presence of either CMV end-organ disease or CMV syndrome and will be confirmed by an independent, blinded 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.

Quantifiable CMV DNAemia is defined as any detected CMV (ie, with a numeric value and 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. 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. The relationship of CMV infection to CMV disease is discussed in Section 5.4.1.1.

The secondary efficacy endpoints are:

1. Proportion of participants with adjudicated CMV disease through 28 weeks post-transplant

   For this endpoint, adjudicated CMV disease will be defined in the same way it is for the primary efficacy endpoint.

2. Time to onset of adjudicated CMV disease through 52 weeks post-transplant

   The time to onset of adjudicated CMV disease will be calculated in days, from the day of randomization to the day of onset of CMV disease as determined by the CAC.

10.4.2 Safety Endpoints

Leukopenia and neutropenia (see Section 5.4.1.3) will be assessed by evaluating the proportion of participants who develop any of the following during the treatment phase. This is specified as a Tier 1 safety endpoint.

1. Report an adverse event of leukopenia
2. Experience total WBC count ≤3,500 cells/μL
3. Report an adverse event of neutropenia
4. Experience ANC ≤1,000 cells/μL

The following are specified as events of interest (Tier-2 safety endpoints):

1. Proportion of participants with any adverse event
2. Proportion of participants with any drug-related adverse event
3. Proportion of participants with any SAE
4. Proportion of participants with any adverse event which is both drug-related and serious
5. Proportion of participants who discontinue due to an adverse event
6. Proportion of participants who report a total WBC count ≤3,500 cells/μL
7. Proportion of participants who report ANC ≤1,000 cells/μL

All AEs will be collected through 14 days after completion of the treatment period. Thereafter, all SAEs related to study medication will be collected through Week 52.

In addition, proportion of male participants with meaningful changes of Inhibin B, FSH, and LH testosterone serum concentrations will be evaluated to monitor testicular function.

10.4.3 Exploratory Endpoints

1. Proportion of participants with quantifiable CMV DNAemia through 28 weeks post-transplant and 52 weeks post-transplant
2. Proportion of participants experiencing allograft dysfunction and/or rejection through 28 weeks post-transplant and 52 weeks post-transplant
    a. Proportion of participants who experience 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. Proportion of participants who experience a biopsy-proven acute renal graft rejection through 28 weeks post-transplant and 52 weeks post-transplant

c. Proportion of participants who experience graft loss through 28 weeks post-transplant and 52 weeks post-transplant

3. Proportion of participants who experience 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.

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

   a. Incidence of all-cause mortality through 28 weeks post-transplant and 52 weeks post-transplant

   b. Incidence and duration of 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. Incidence of select OIs (see Section 9.10.1) through 28 weeks post-transplant and 52 weeks post-transplant

   d. Proportion of participants who report 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.

5. Antiviral resistance to LET in prophylaxis failures through 52 weeks post-transplant (see Section 9.5.8.3 for details)

6. Glycoprotein B (gB) genotype of CMV in prophylaxis failures through 52 weeks post-transplant (see Section 9.5.8.4 for details)

7. Genetic analyses (see Section 5.4.1.5 for details)

8. Patient-reported outcomes (EQ-5D and SF-36v2® scores)

9. Pharmacokinetic endpoints, including the evaluation of exposure-response relationships with selected efficacy and safety endpoints (reported in a separate Modeling and Simulation report; see Section 10.6.3.2 for details)

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

10.5 Analysis Populations

10.5.1 Efficacy Analysis Populations

Full Analysis Set (FAS)

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who received at least one dose of study treatment, are D+/R-, and had no detectable CMV viral DNA (measured by central laboratory) on Day 1.

Per Protocol (PP)

The PP population will serve as a supportive analysis population. The PP population excludes participants due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints.

Potential violations that may result in the exclusion of a participant from the PP population include:

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

The final determination on protocol violations will be made prior to the final unblinding of the database and will be documented in a protocol violator memo.

Participants will be included in the treatment arm to which they are randomized for the analysis of efficacy data using both the FAS and PP populations.

10.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment arm corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most participants this will be the treatment arm to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment arm corresponding to the study treatment actually received.

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

10.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 10.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 10.8, Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

10.6.1 Statistical Methods for Efficacy Analyses

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

10.6.1.1 Primary Efficacy Analysis

To test the primary hypothesis that LET is non-inferior to VGCV in the prevention of CMV disease, the difference between the two treatment arms in the proportions of participants with adjudicated CMV disease through 52 weeks post-transplant and the associated two-sided 95% CI will be calculated using the stratum-adjusted Mantel-Haenszel method with stratification by highly cytolytic anti-lymphocyte therapies. LET will be concluded to be non-inferior to VGCV if the upper bound of the two-sided 95% CI for the difference in proportion of participants with adjudicated CMV disease (LET - VGCV) is no higher than 0.10.

Exposure to the lower LET IV dose (240mg without concomitant CsA) is not expected to impact the primary efficacy analysis. For subjects randomized to receive IV LET (including 240mg or 480mg without concomitant CsA and 240mg with concomitant CsA), the percentage of time exposed to IV LET is anticipated to be minimal. Efficacy of the LET IV 240 mg (with and without concomitant CsA) and LET IV 480 mg (without concomitant CsA) groups may be assessed in an exploratory manner.

The primary efficacy analysis will be performed on the FAS population, with the PP population considered a supportive approach. A sensitivity analysis including those participants who were assessed by the investigator to have CMV disease regardless of the CAC determination will be performed. An additional sensitivity analysis will be performed where any participant who discontinues study treatment but thereafter is started on CMV prophylaxis at the discretion of the investigator is considered a failure.

Provided non-inferiority is established, a hypothesis that LET is superior to VGCV in the prevention of CMV disease will be tested. The stratum-adjusted Mantel-Haenszel method (with continuity correction) will be used to compare the two treatment arms with respect to the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant using the stratification factor of highly cytolytic anti-lymphocyte therapies. LET will be concluded to be superior to VGCV if the upper bound of the two-sided 95% CI

for the difference in proportion of participants with adjudicated CMV disease (LET - VGCV) is less than 0.

10.6.1.2 Secondary Efficacy Analyses

To assess the difference in the proportion of participants with adjudicated CMV disease through 28 weeks post-transplant, similar to the primary endpoint the difference between arms and the associated 95% CI will be calculated using the stratum-adjusted Mantel-Haenszel method with stratification by highly cytolytic anti-lymphocyte therapies. Formal hypothesis testing will be done on this endpoint in the event that the second primary hypothesis of superiority is met.

Time to onset of adjudicated CMV disease through 52 weeks post-transplant will be estimated using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted by treatment arm and a p-value for the between arm difference in time to onset of adjudicated CMV disease will be provided using the stratified log-rank test with stratification by highly cytolytic anti-lymphocyte therapies. Observations will be censored at the time of discontinuation from the study, or at completion of the study.

10.6.1.3 Missing Data Handling

There are two types of missing values:

- Intermittent missing values due to a missed or skipped visit. Note that this does not apply to the primary endpoint which is at the end of the trial but 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 missing due to premature discontinuation from the study

Table 13 provides a summary of approaches to handle missing values.

Table 13 Summary of Approaches to Handle Missing Values

Approach	Intermittent Missing	Monotone Missing
NC = F	Failure	Failure
OF	Excluded	No failure
F = failure; NC = non-completer; OF = observed failure.		

The primary missing data approach will be the Observed Failure (OF) approach. Using this approach, participants who discontinue prematurely from the study for any reason are not considered failures.

The Non-Completer = Failure (NC = F) approach will be used as a supportive analysis. Non-completers refers to participants who prematurely discontinue from the study for any

reason without having developed CMV disease. Using the NC = F approach, these participants will also be considered failures.

Additional analysis to evaluate the potential effect of violations in assumptions about the missing data may be performed.

Table 14 summarizes the key efficacy analyses.

Table 14 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Timepoint)	Primary Versus Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach[*]
Primary Hypothesis/Endpoint				
Proportion of participants with adjudicated CMV disease through 52 weeks post-transplant	P	Stratified M&H[‡]	FAS	OF
	S	Stratified M&H[‡]	FAS	NC = F
	S	Stratified M&H[‡]	PP	OF
Secondary Endpoints				
Proportion of participants with adjudicated CMV disease through 28 weeks post-transplant	P	Stratified M&H[‡]	FAS	OF
	S	Stratified M&H[‡]	FAS	NC = F
Time to onset of adjudicated CMV disease through 52 weeks post-transplant	P	Kaplan-Meier	FAS	N/A

[†]P = Primary approach; S = Supportive approach.

[*] OF = observed failure; M&H = Mantel-Haenszel method; NC =F = non-completers equal failure; N/A = not applicable.

[‡]Stratum-adjusted Mantel-Haenszel method with stratification by highly cytolytic anti-lymphocyte therapies

10.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 15). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-arm comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-arm comparisons; only point estimates by treatment arm are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change (PDLC) in laboratory parameters that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 participants in any treatment arm exhibit the event; all other adverse experiences and PDLC will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-arm difference in percent incidence will always include zero when treatment arms of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-arm differences in adverse experiences and PDLC.

P-values (Tier 1 only) and 95% CIs (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method - an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985] and will not be stratified. All AEs will be analyzed through the end of the treatment period. Drug-related SAEs which are collected throughout the study will also be analyzed through Week 52.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-2 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 15 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Reporting any of the following: AE of leukopenia, total WBC count ≤3,500 cell/μL, AE of neutropenia, ANC ≤1,000 cell/μL	X	X	X
Tier 2	Any AE		X	X
	Any serious AE		X	X
	Any drug-related AE		X	X
	Any serious and drug-related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 participants in one of the treatment arms)		X	X
	Total WBC count ≤3,500 cell/μL		X	X
	ANC ≤1,000 cells/μL		X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 participants in both treatment arms)			X
	Change from baseline results (laboratories, ECGs, vital signs)			X

AE = adverse event; ANC = absolute neutrophil count; CI = confidence interval; ECG = electrocardiogram; SOC = System Organ Class; PDLC = predefined limit of change; WBC = white blood cell; X = results will be provided.

10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

10.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment arms for each relevant characteristic will be assessed by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized, and the primary reasons for screening failure, and discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, indication for kidney transplant, transplant and dialysis or plasmapheresis details (see Section 9.1.6), and prior and concomitant therapies will be summarized by treatment arm using descriptive statistics for continuous or categorical variables, as appropriate.

10.6.3.2 Pharmacokinetic Analyses

The PK data obtained from this study will be used to characterize the PK of LET in kidney transplant recipients and evaluate exposure-response relationships with selected efficacy and safety endpoints including dose for those participants not on concomitant CsA and requiring IV dosing. The prospective details of this analysis will be specified in a separate Modeling and Simulation analysis plan.

10.7 Interim Analyses

No interim analyses for efficacy are planned for this study. However, to ensure safe study conduct, an independent unblinded external Data Monitoring Committee (DMC) will be established. The DMC will convene to review safety data approximately every 6 months during the study.

10.8 Multiplicity

The primary efficacy hypothesis for non-inferiority will be tested at a two-sided alpha level of 5% because no interim efficacy analyses will be performed. If the primary efficacy hypothesis testing for non-inferiority of LET is met, the second primary hypothesis of superiority will be tested at the two-sided Type I error rate of 5%. If the second primary hypothesis of superiority is met, similar step-down hypothesis testing will be performed for the secondary endpoint of adjudicated CMV disease through 28 weeks post-transplant. Other efficacy analyses will be considered secondary or explanatory.

10.9 Sample Size and Power Calculations

10.9.1 Sample Size and Power for Efficacy Analyses

Three hundred (300) participants will be randomized into each treatment arm for a total of 600 participants. Assuming the true proportion of participants with adjudicated CMV disease is 0.17 for both treatment arms, this study has 90% power to demonstrate that LET is non-inferior to VGCV at an overall two-sided 5% alpha-level, using a non-inferiority margin of 0.10. See section 5.4.1.1.3 for the rationale for the non-inferiority margin. The minimum criterion for success is that the upper bound of 95% CI of difference (LET minus VGCV) <0.10. The observed proportion of participants in the LET arm needs to be less than 4% higher than that in the VGCV arm in order to declare non-inferiority. If the observed proportion of participants in the LET arm is approximately 9% lower than in the VGCV arm, this is expected to demonstrate superiority with 90% power.

The adjudicated CMV disease incidence of 17% is supported by the results of the IMPACT study. In this study, the primary efficacy endpoint was the proportion of D+/R– participants who developed CMV disease (as defined in Appendix 7) adjudicated by the CAC.

10.9.2 Sample Size and Power for Safety Analyses

Table 16 summarizes the percentage point differences between the 2 treatment arms that could be detected with 90% probability for a variety of hypothetical underlying incidences of leukopenia (reported as AE) in the LET arm. These calculations assume 300 participants in each treatment arm and are based on a 1-sided 2.5% alpha level. The reported incidence of leukopenia AE in the IMPACT study is 38% for 200 days of VGCV [Humar, A., et al 2010]. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. 1990].

Table 16 Power to Show Superiority for a Variety of Hypothetical Underlying Incidences of Leukopenia Adverse Events (n = 300/arm)

	Power to Show Superiority with n=300/arm					
	LET Rate					
VGCV Response rate	**18**	**20**	**22**	**24**	**26**	**28**
30	93	81	61	<40	<40	<40
34	>99	97	91	78	57	<40
38	>99	>99	99	96	89	75
42	>99	>99	>99	>99	99	95
LET = letermovir; VGCV = valganciclovir						

10.10 Subgroup Analyses

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

- Age category (≤65 versus >65 years)
- Sex (female, male)
- Race (white, non-white)
- Induction therapy (use, non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction)
- Region (US, Ex-US)

Other clinically relevant variables may be identified for which additional subgroup analyses may be performed.

Sample sizes within subgroups will be smaller than the overall trial sample size; therefore, estimation may not be precise and the 95% CIs may be wide. If any subgroup category has less than 15 participants in either treatment arm then only descriptive statistics will be displayed (no estimate of treatment difference and no CIs). If there are less than 15 participants in either treatment arm, the subgroup category will not be displayed in the forest plot.

10.11 Compliance (Medication Adherence)

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

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

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

Compliance rates will be summarized for each treatment arm and individual compliance rates will factor into the identification of protocol violators as discussed in Section 10.5.1.

10.12 Extent of Exposure

The extent of exposure of study treatment will be evaluated by summary statistics for the "Number of Days on Therapy" by treatment arm.

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation/Term	Definition
ACV	Acyclovir/aciclovir
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASaT	All Subjects 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
BID	Twice daily
BSA	Body surface area
CAC	Clinical Adjudication Committee
CBC/diff	Complete blood count with differential
CI	Confidence interval
CMV	Cytomegalovirus
CrCl	Creatinine clearance
CsA	Cyclosporin A
CSR	Clinical Study Report
DB	Dense body
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DNAemia	Detection of DNA in samples of plasma, whole blood, and isolated peripheral blood leukocytes or in buffy-coat specimens.
DNQ	Detected, Not Quantifiable
ECG	Electrocardiogram
ECI	Event of clinical interest
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EQ	EuroQol

Abbreviation/Term	Definition
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte colony-stimulating factor
gB	Glycoprotein B
GCV	Ganciclovir
HBsAg	Hepatitis B surface antigen
HCV-Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International normalized ratio
IRB	Institutional Review Board
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Integrated web response system
KDIGO	Kidney Disease Improves Global Outcomes
LAM	Lactational amenorrhea method
LET	Letermovir
LH	Luteinizing hormone
LLoQ	Lower limit of quantification
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
MMF	Mycophenolate mofetil
NA	Not applicable
NODAT	New onset diabetes mellitus after transplant

Abbreviation/Term	Definition
NTR	Narrow therapeutic range
OF	Observed Failure
OI	Opportunistic infection
PCR	Polymerase chain reaction
PCS	Physical Component Summary
PDLC	Predefined limits of change
PET	Pre-emptive therapy
P-gp	P-glycoprotein
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetic
PO	Orally
PRO	Patient-reported outcome
PT	Prothrombin time
QD	Once daily
QoL	Quality of life
γ-IFN	γ-interferon
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCR	Screening
SF-36v2®	36-Item Short Form Health Survey Version 2.0
SoA	Schedule of activities
SOC	Standard of care
SOT	Solid organ transplant
Tp	Transplant
TRD	Treatment-related discontinuation
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
VGCV	Valganciclovir
VZV	Varicella zoster virus
WBC	White blood cell

Abbreviation/Term	Definition
WHO	World Health Organization
WOCBP	Woman of childbearing potential

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 17 will be performed by the central laboratory unless otherwise specified within the protocol.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 6.1 and 6.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 17 Protocol-Required Safety Laboratory Assessments

Hematology[a]	Chemistry[a]	Urinalysis[a]	Other
Hematocrit	Albumin	Blood	FSH, LH, testosterone, and Inhibin B levels in males
Hemoglobin	Alkaline phosphatase	Glucose	Urine β-hCG[e]
Platelet count	ALT	Protein	HBsAg[b]
WBC (total and differential)	AST	Specific gravity	HCV-Ab[b]
	Bicarbonate	Microscopic examination, if abnormal results are noted	Hepatitis C RNA PCR[b]
	Calcium		HIV antibody[b]
	Chloride		CMV DNA PCR[c]
	Creatinine		CMV viral resistance testing[d]
	Creatinine Clearance		QuantiFERON-CMV Assay
	Glucose		Coagulation: PT/INR[a]
	Phosphorus		eGFR calculation
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin		
	Indirect Bilirubin		
	Total protein		
	Blood Urea Nitrogen		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; CMV = cytomegalovirus; FSH = follicle-stimulating hormone; HBsAg = Hepatitis B surface antigen; HCV-Ab = Hepatitis C virus antibody; HIV = human immunodeficiency virus; IgG = immunoglobulin G; INR = International normalized ratio; LET = letermovir; LH = luteinizing hormone; PCR = polymerase chain reaction; PT = prothrombin time; 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 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 randomization 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 who discontinue study treatment due to CMV disease or in whom study medication is stopped and CMV treatment is started.
e. May use local or central laboratory serum pregnancy test if unable to provide urine.

Investigators must document their review of each laboratory safety report.

Table 18 summarizes the approximate blood volumes collected by study visit and sample types.

Table 18 Approximate Blood/Tissue Volumes Drawn/Collected by Study Visit and by Sample Types

Study Period	Pre-Treatment	Treatment												Follow-up						CMV Disease 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]	4	4	4		4		4		4	4	4	4	4	4						4
Coagulation[a]	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5						4.5
Serum Inhibin B, LH, FSH, Testosterone Levels in Men		12											12						12	12
HIV and Hepatitis B and C Screen[b]	16																			
Blood for Genetic Analysis	8.5																			
CMV DNA PCR[c]		4		4	4		4		4	4	4	4	4	4	4	4	4	4	4	4
CMV serology (IgG)	X[d]																			
QuantiFERON-CMV Assay	3								3				3			3			3	3
CMV Viral Resistance Testing/gB Genotypic Testing[e]																			10	10[f]
Population PK		5	5	5	5	5	5	5	5	5	5	5	5							5
Intensive PK at Week 1 for: -participants of Asian descent; and -for participants of non-Asian descent who consent to intensive PK			25																	
Intensive PK (during IV administration for >5 consecutive days)			←----------25 (performed at most once during the study; this volume is NOT included in the Expected Total volume)----------→																	
Expected Total (mL)	38+X	31.5	40.5	13.5	19.5	9.5	19.5	9.5	22.5	19.5	19.5	19.5	34.5	14.5	4	7	4	4	29	44.5

Study Period	Pre-Treatment	Treatment												Follow-up						CMV Disease 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**	

CMV = cytomegalovirus; D = Day; DNA= deoxyribonucleic acid; FSH = follicle-stimulating hormone; gB = glycoprotein B; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IV = intravenous; LET = letermovir; LH = luteinizing hormone; 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 randomization 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. Only if not previously documented within 180 days prior to randomization (see Section 6.1, Inclusion Criteria). Performed locally per SOC at the site.
e. To be performed only for participants who discontinue study treatment due to CMV disease or in whom study medication is stopped and CMV treatment is started. DNA extracted from the plasma samples used for CMV viral resistance testing will be used for the CMV UL55 (gB) genotypic testing.
f. A repeat sample should be collected at the next scheduled visit after the CMV disease visit.

12.3 Appendix 3: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, 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 participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck 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 which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

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 Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck 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. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck 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

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

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck 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.

Merck does not pay for participant referrals. However, Merck 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 Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck 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 including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

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.

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 which 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.

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 institutional review board, ethics review committee (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 trial 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.

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 trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form 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 trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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.

Committees Structure

Scientific Advisory Committee

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

Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the trial.

Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

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

Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 10 – Statistical Analysis Plan, as well as evaluating the presence of confounding factors.

1) CMV disease, as defined in Appendix 7: This role is important to standardize the evaluation (ie, adjudication) of all suspected cases of CMV disease occurring during the trial.

All personnel involved in the adjudication process will remain blinded to study treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the Adjudication Charter.

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.

Compliance with Trial 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 trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov,

www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial 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 trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

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

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

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

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.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

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

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

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

Source Documents

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

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • 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 treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are 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 treatment 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 treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, 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 9.3.5 for protocol specific exceptions

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

A 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient'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) which 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 one 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.

Additional Events reported

Additional Events which require reporting
● In addition to the above criteria, adverse events 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.

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 Adverse Event case report forms/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 trials, awareness of symptoms, but easily tolerated)
  - Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric trials, 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 utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric trials, extremely distressed or unable to do usual activities).

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event 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 adverse event 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 adverse event:

  - **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 trials 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 trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

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

    - 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH 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 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment 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 one 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.

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

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

● The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  ● Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  ● If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  ● Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection 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 Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF
● If the electronic data collection 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 Trial File Binder (or equivalent).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal 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 non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 6.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- 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 condom with cap, diaphragm or sponge with spermicide.
  - Male and female condom cannot be used together.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 19 during the protocol-defined time frame in Section 6.1.

Table 19 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progesterone-only implant[a] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

Pregnancy Testing

Women of childbearing potential should only be included after a negative highly sensitive urine or serum pregnancy test (per SOC at the site) and in accordance with local requirements.

Following initiation of treatment, additional pregnancy testing will be performed at monthly intervals during the treatment period, 4, 8, 12 weeks after the last dose of study treatment for participants who complete the treatment period, and at CMV disease visit and/or early discontinuation visit.

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

12.6 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

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Samples 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

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

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 trial 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 trial site under secure storage for regulatory reasons.

A template of each trial 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 electronic Case Report Forms (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 trial purposes.

4. Confidential Participant Information for Future Biomedical Research

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 trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment 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 trial 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 trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

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 this sub-trial. 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

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 principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial 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

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 trial 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 trial, the trial 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

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial 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

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

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For Future Biomedical Research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (ie, only leftover samples are being retained).

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 e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

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

12.7 Appendix 7: 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.
Hepatitis	N/A	Abnormal liver function tests **AND** CMV documented in tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques **AND** Absence of other documented cause of hepatitis	• Detection of CMV by PCR alone is insufficient as it may represent transient DNAemia. Hence, PCR is insufficient to diagnose CMV hepatitis. • Documentation of CMV in liver biopsy specimen (ie, by culture, histopathology, immunohistochemical analysis or *in situ* hybridization) is needed. • Coinfection with other pathogens like HCV may be present without excluding the diagnosis of CMV hepatitis.

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

CMV Disease Type	Probable	Proven	Notes
Pancreatitis	N/A	Detection of CMV by virus isolation, rapid culture, immunohistochemistry, or *in situ* hybridization in a pancreatic biopsy specimen obtained from a patient with pancreatitis AND Identification of conventional histologic features of CMV infection	N/A
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]

12.8 Appendix 8: Child-Pugh Classification for Severity of Liver Disease

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

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

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

INR = international normalized ratio

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

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