Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation

Supplementary Appendix

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2. Glossary of certain terms and definition used in the full protocol document

- **Full Analysis Set (FAS)**, refers to the *Primary Efficacy Population* which includes all randomized patients who received study treatment and had no detectable CMV DNA in plasma on the day of randomization.
- **All Subjects as Treated (ASaT)** population: refers to the *Safety Population* which includes all randomized patients who received one or more doses of study drug.
- **Non-completers= Failure (NC=F),** was an statistical approach to missing data in which any patient who prematurely discontinued from the study was considered a failure (event) for the primary endpoint analysis and other analyses in the trial.
- **Data-as-observed approach (DAO),** used the data generated by a patient in the trial until the time of premature discontinuation, censoring the patient at the time of discontinuation. This approach was used in some secondary endpoint and exploratory analyses in the trial.

3. Full eligibility criteria

3.1 Inclusion criteria

To be eligible for participation in this trial, the patient must:

1. be ≥ 18 years of age on the day of signing informed consent.
2. have documented seropositivity for cytomegalovirus (CMV) (recipient CMV IgG seropositivity [R+]) within 1 year before hematopoietic-cell transplantation (HCT).
3. be receiving a first allogeneic HCT (bone marrow, peripheral blood stem cell, or cord blood transplant).
4. have undetectable CMV DNA (as confirmed by the central laboratory) from a plasma sample collected within 5 days prior to randomization.
5. be within 28 days post-HCT at the time of randomization.
6. be highly unlikely to become pregnant or to impregnate a partner since they meet at least one of the following criteria:
    a. A female patient who is not of reproductive potential is eligible without requiring the use of contraception. A female patient who is not of reproductive potential is defined as one who: (1) has reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] levels in the postmenopausal range as determined by the local laboratory, or 12 months of spontaneous amenorrhea); (2) is 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or (3) has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (e.g., anorexia nervosa).
    b. A male patient who is not of reproductive potential is eligible without requiring the use of contraception. A male patient who is not of reproductive potential is defined

as one whom has undergone a successful vasectomy. A successful vasectomy is defined as: (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy.

c. A male or female patient who is of reproductive potential agrees to true abstinence or to use (or have their partner use) 2 acceptable methods of birth control starting from the time of consent through 90 days after the last dose of study therapy. Longer periods of birth control may be required per local requirements. True abstinence is defined as abstinence in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., abstinence only on certain calendar days, abstinence only during ovulation period, use of symptothermal method, use of post-ovulation methods) and withdrawal are not acceptable methods of contraception. Acceptable methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, and vasectomy OR use of appropriate double barrier contraception as per local regulations or guidelines. Hormonal contraceptives (e.g., birth control pills, transdermal patch, or injectables) are unacceptable methods of birth control for use in this study because it is not known whether these methods are affected by co-administration of letermovir.

7. be able to read, understand, and complete questionnaires and diaries.
8. understand the study procedures, alternative treatment available, and risks involved with the study, and voluntarily agree to participate by giving written informed consent. The patient may also provide consent for Future Biomedical Research. However, the patient may participate in the main trial without participating in Future Biomedical Research.

3.2 Exclusion criteria

The patient must be excluded from participating in the trial if the patient:

1. received a previous allogeneic HCT (Note: Receipt of a previous autologous HCT is acceptable).
2. has a history of CMV end-organ disease within 6 months prior to randomization.
3. has evidence of CMV viremia (if tested) at any time from either signing of the ICF or the HCT procedure, whichever is earlier, until the time of randomization. (Note: Evidence of CMV viremia as reported by central lab will include reporting of test results as "detectable, not quantifiable" or "detected" with a numeric value provided.)
4. received within 7 days prior to screening or plans to receive during the study any of the following:
    - ganciclovir
    - valganciclovir
    - foscarnet
    - acyclovir (at doses > 3200 mg PO per day or > 25 mg/kg IV per day)
    - valacyclovir (at doses > 3000 mg PO per day)
    - famciclovir (at doses > 1500 mg PO per day)
5. received within 30 days prior to screening or plans to receive during the study any of the following:
    - cidofovir
    - CMV hyper-immune globulin
    - Any investigational CMV antiviral agent/biologic therapy

6. has suspected or known hypersensitivity to active or inactive ingredients of letermovir formulations.
7. has severe hepatic insufficiency (defined as Child-Pugh Class C; see Appendix 12.5) within 5 days prior to randomization.
8. has serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x the upper limit of normal (ULN) or serum total bilirubin > 2.5 x ULN within 5 days prior to randomization.

   Note: Patients who meet this exclusion criterion may, at the discretion of the investigator, have one repeat testing done prior to randomization. If the repeat value does not meet this criterion, they may continue in the screening process. Only the specific out of range value should be repeated (not the entire panel).
9. has end-stage renal impairment with a creatinine clearance less than 10 mL/min, as calculated by the Cockcroft-Gault equation using serum creatinine within 5 days prior to randomization

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

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

   Note: Patients who meet this exclusion criterion may, at the discretion of the investigator, have one repeat testing done within 5 days prior to randomization. If the repeat value does not meet this criterion, they may continue in the screening process. Only the specific out of range value should be repeated (not the entire panel).
10. has both moderate hepatic insufficiency AND moderate renal insufficiency.

    Note: Moderate hepatic insufficiency is defined as Child Pugh Class B (see Appendix 12.5); moderate renal insufficiency is defined as a creatinine clearance less than 50 mL/min, as calculated by the Cockcroft-Gault equation (as above), respectively.

11. has an uncontrolled infection on the day of randomization.
12. requires mechanical ventilation or is hemodynamically unstable at the time of randomization.
13. has a documented positive result for a human immunodeficiency virus antibody (HIV-Ab) test at any time prior to randomization, or for hepatitis C virus antibody (HCV-Ab) with detectable HCV RNA, or hepatitis B surface antigen (HBsAg) within 90 days prior to randomization.
14. has active solid tumor malignancies with the exception of localized basal cell or squamous cell skin cancer or the condition under treatment (e.g., lymphomas).
15. is pregnant or expecting to conceive, is breastfeeding, or plans to breastfeed from the time of consent through 90 days after the last dose of study therapy.
16. is expecting to donate eggs or sperm starting from the time of consent through 90 days after the last dose of study therapy.
17. is currently participating or has participated in a study with an unapproved investigational compound or device within 28 days, or 5X half-life of the investigational compound (excluding monoclonal antibodies), whichever is longer, of initial dosing on this study. Patients previously treated with a monoclonal antibody will be eligible to participate after a 28-day washout period.

    Note: Investigational chemotherapy regimens involving approved agents and investigational antimicrobial regimens involving approved antibacterial/antifungal/antiviral agents, investigational radiotherapy studies, or other observational studies are allowed.
18. has previously participated in this study or any other study involving letermovir.

19. 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.
20. is or has an immediate family member (spouse or children) who is investigational site or Sponsor staff directly involved with this trial.
21. 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: Patient who has a history of recreational marijuana use which is not deemed excessive by the patient's investigator or does not interfere with the patient's daily function may participate in the study but must be instructed to discontinue any further use of recreational marijuana prior to entry into trial and throughout the trial period.
22. 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 patient's participation for the full duration of the study, or would be put at undue risk as judged by the investigator, such that it is not in the best interest of the patient to participate in this study.

4. Stratification criteria at time of randomization

Patients were stratified by 1) study center and 2) risk for CMV reactivation and CMV disease. Risk factor groups include 2 categories as defined below:

a. **High risk**: Patients meeting one or more of the following criteria at the time of randomization:

- Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR,
- Haploidentical donor,
- Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1,
- Use of umbilical cord blood as stem cell source,
- Use of ex vivo T-cell-depleted grafts (including ex vivo use of alemtuzamab [Campath™]),
- Grade 2 or greater graft-versus-host disease (GVHD), requiring the use of systemic corticosteroids (defined as the use of ≥ 1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).

b. **Low risk**: All patients not meeting definition of high risk

5. Rationale for dose selection for this phase 3 trial

Phase I studies demonstrated that coadministration of letermovir with cyclosporine increased letermovir exposure ~3 fold. Further analyses using the Phase IIB study data indicated that exposure with the 240 mg dose of letermovir administered without cyclosporine overlapped with exposure levels of the 60 and 120 mg once-daily doses, which were associated with virologic failures. Most such failures occurred at letermovir levels with AUC_{tau} values < 45,000 ng×h/mL. Consequently, an efficacy target for success in > 90% of the patients was set at AUC_{tau} levels ≥ 45,000 ng×h/mL. It is predicted that this target level would be achieved with a dose of 240 mg of letermovir once daily in patients receiving cyclosporine, and with 480 mg of letermovir once daily in the absence of concomitant cyclosporine use. Modeling and simulation data indicated that exposure levels of letermovir with the 480 mg dose in the absence of cylcosporine will not exceed exposure levels seen with the 240 mg dose of letermovir when administered with cyclosporine in the Phase IIB data (n=18). These exposure levels were not also associated with any significantly increased adverse events when compared to placebo used in the study.
Based on all available safety data, letermovir efficacy in the Phase 2 studies, and the exposure-response data, this study used a dose of 240 mg daily for patients receiving cyclosporine and 480 mg daily in patients who are not receiving cyclosporine concomitantly.

6. Pharmacokinetic Evaluations

Population (sparse) Pharmacokinetic (PK) samples were collected in all patients. Nine planned samples were to be collected 0-2 hours pre-dose at the Day 1, Day 7, Weeks 2, 4, 6, 8, 10, 12, and 14 visits. As treatment may range 10 – 14 weeks, the Week 12 and 14 visit samples may not have been collected in all patients.

Intensive PK sampling was performed in a subset of 75 patients on letermovir who consented to this optional testing. Five samples were collected at the Day 7 visit (i.e., on Days 5-9 after starting study therapy) at the following time points: pre-dose, 1 hour (± 10 min) following oral administration (or within 10 min after infusion completion, when given IV), 2.5 hours following oral/IV administration (± 30 min), 8 hours following oral/IV administration (range of 6-10 hours), and 24 hours following oral/IV administration (range of 22-24 hours; 0-2 hours prior to next day's dose).

Letermovir concentrations were measured using liquid chromatography-mass spectrometry/ mass spectrometry (LC-MS/MS) at Quintiles Q^2 Solutions B.V. (Oss, The Netherlands).

7. CMV DNA PCR Testing

CMV DNA PCR testing was performed using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) assay at the central laboratories (Quest Diagnostics Clinical Trials, Valencia, California, USA; and Quest Diagnostics Limited, Heston, Middlesex, UK). The assay had a lower limit of quantitation of 151 copies/mL (137 IU/mL). One IU/mL of CMV DNA is approximately 1.1 copies/mL in this assay.

Samples were collected at every study visit and sent to the central laboratory. CMV DNA PCR testing could be conducted within 3 days prior to a scheduled study visit and no later than the day of the scheduled study visit. (This CMV DNA PCR testing window was not applicable to a CMV Infection Visit).

It was mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory immediately prior to (i.e., on the day of) initiating treatment for CMV disease or PET. Results from this confirmatory plasma sample did not need to be available to initiate treatment. If the confirmatory result obtained on the day of PET initiation was NOT available

(e.g., sample is lost or mishandled by the investigator site prior to shipment, or is inadequate upon receipt at the central laboratory), a subsequent sample had to be obtained and sent to the central laboratory within 7 days after PET initiation (preferably within 48-72 hours). The patient was considered to have met the primary efficacy endpoint if this confirmatory laboratory result was positive.

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

8. CMV DNA Sequence Analysis

CMV DNA sequence analysis was attempted on DNA isolated from plasma samples obtained from all patients enrolled in the study who meet the criteria for clinically significant CMV infection with documented viremia. Resistance to letermovir was monitored by genotypic analysis of the CMV terminase complex genes UL56 and UL89. Samples were analyzed by PCR amplification and next-generation DNA sequencing at DDL Diagnostic Laboratory B.V. (Rijswijk, The Netherlands). For nearly all patients, the sample used for genotypic analysis was collected within 7 days of the initiation of PET or diagnosis of end-organ disease. Additional UL56/UL89 genotypic analyses will be performed using alternate plasma samples collected on or near the day when PET was initiated

Based on *in vitro* selection and characterization of mutant viruses that escape inhibition by letermovir, several substitutions in the UL56 protein have been confirmed as necessary and sufficient for resistance to letermovir. No letermovir resistance associated mutations have been

identified in other CMV genes, including those encoding other presumed terminase subunits (such as UL89). However, previous studies with structurally unrelated CMV terminase inhibitors have identified mutations in the UL89 gene that confer resistance to those compounds, so the UL89 gene was included in the genotypic analysis.

All genotypic variants encoding amino acid substitutions in UL56 and UL89 that have not been previously described or characterized are candidates for phenotypic analysis. Using a marker transfer technique, these variants will be introduced into a wild-type CMV background and susceptibility to letermovir and other anti-CMV agents will be measured. This analysis will be described separately.

9. Future Biomedical Research, Pharmacogenomic Analysis

The following specimens are to be obtained as part of Merck's Future Biomedical Research (FBR) platform that was incorporated into the study:

- Leftover DNA for future research
- Leftover main study plasma collected for CMV DNA PCR for future research

The protocol contemplated using Merck's central FBR platform to collect DNA samples to conduct a pharmacogenomics analysis related to letermovir's metabolism. Patients provided a separate consent to have DNA stored for this and any future analyses the sponsor may want to conduct. The central FBR platform required that blood samples for DNA storage be collected on the day of randomization to minimize certain biases. As most patients in the trial began study drug before engraftment, most samples contained little to no patient's DNA for these pharmacogenomics analyses. In addition, the samples collected from patients who began treatment after engraftment contained predominantly donor DNA, making any inferences about

the recipient's pharmacogenomics, especially those related to liver metabolism, impossible. Given these circumstances, no pharmacogenomics analyses were performed in this trial.

10. Deviations from eligibility criteria among randomized study patients.

Deviations from eligibility criteria were noted in 51 (9%) of patients randomized into the study (more than one reason was noted in 6 patients):

- 28 patients had central laboratory screening tests missing or done outside the five-day screening window.
- 16 patients had plasma CMV DNA detected prior to randomization.
- 6 patients had other screening laboratory results outside the protocol-specified eligibility ranges.
- 2 patients were participating in clinical trials using other investigational compounds.
- 2 patients were randomized using local laboratory results instead of central laboratory results.
- 1 patient had no documented CMV seropositivity within one year prior to HCT (the patient was CMV-seropositive).
- 1 patient had received a prior allogeneic HCT.
- 1 patient was CMV-seronegative.

11. Post-hoc analysis of the Week 24 Clinically-Significant CMV Infection endpoint using other approaches to missing data and imputed failures than the non-completers considered failures approach.

As additional analyses following the guidance of the Journal's statistical reviewer, a multiple imputation model was carried out within each risk strata to impute the occurrence of clinically significant CMV infection in those subjects who either discontinued from the study before Week 24 or were missing a visit in the critical outcome window.[1,2]

Two assumptions for missing data were made: missing-at-random (MAR) and missing-not-at-random (MNAR). Under MAR, the imputation model assumed the clinically significant CMV infection (CS-CMVi) rate = the observed rate for each treatment group. Under MNAR, the imputation model assumed the CS-CMVi rate for both letermovir and placebo groups = the observed rate in the placebo group. The imputations generated 500 complete datasets, where outcomes were imputed within strata for all patients with missing outcome. A logistic regression model for monotone missing data and a random number generator were used to impute the missing data.

Using the MAR approach, the stratum-adjusted treatment difference was -30.7 (95% CI: -34.8, -26.5), $p<0.0001$, between letermovir and placebo. The point estimate for the failure rate among letermovir subjects was 21.7% (95% CI: 16.7, 26.7) and the point estimate for the failure rate among placebo subjects was 51.7 (95% CI: 42.0, 60.0).

Using the MNAR approach, the stratum-adjusted treatment difference is -24.5 (95% CL: -28.4, -20.7, $p<0.0001$) and the point estimate for the failure rate among letermovir subjects is 28.1% (95% CL: 22.3, 33.7) and the point estimate for the failure rate among placebo subjects is 51.8 (95% CL: 43.6, 60.1).

12. Post-study Mortality Analysis requested by the FDA

After review of the mortality data submitted to the US Food and Drug Administration (FDA) and reported in this article, the FDA requested an additional analysis including vital status for subjects who prematurely withdrew from the study. As this was a post-study, not on protocol analysis requested after the trial had been closed, some country and local ethics committees (IRBs) did not allow investigators to go back and obtain this information. Merck and study site investigators were able to collect vital status for 58 of the 76 subjects who prematurely withdrew from the trial with unknown mortality status. Ultimately, vital status information was available for 96.8% (547/565) of the safety population.

Including this post-study mortality information, the Kaplan-Meier (K-M) event rate for all-cause mortality at Week 24 post-transplant was lower for the letermovir group (12.1%; 95% CI, 8.6% to 15.7%) compared to the placebo group (17.2%; 95% CI, 11.5% to 22.9%). The distribution of time to all-cause mortality was substantially different between the groups (nominal two-sided p-value = 0.0401, stratified log-rank test). The K-M event rate for all-cause mortality at Week 48 post-transplant (including post-study information), was lower for the letermovir group (23.8%; 95% CI, 19.1% to 28.5%) compared to the placebo group (27.6%; 95% CI, 20.8% to 34.4%). The absolute difference in mortality between letermovir and placebo (approximately 4-5%) was maintained from Week 24 through Week 48. For the distribution of time to all-cause mortality through Week 48 (letermovir vs. placebo), the nominal two-sided p-value was 0.2117 (stratified log-rank test). These data are those presented in the FDA label for letermovir."

Supplementary Tables

Table S1. Study assessments, by study visit.

Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	Screen	Treatment (Week 1)		Treatment (Weeks 2 to 14[c])													Post-treatment Follow-up (Weeks 15 to 24[c])					Post-treatment Follow-up (Weeks 25 to 48[c])			
Week No. (unless otherwise indicated)	SCR[a]	Day 1[b]	Day 7	2	3	4	5	6	7	8	9	10[d]	11[d]	12[d]	13[d]	End of Study Therapy Visit 14[d]	16	18	20	22	24	32	40	48	CMV Infection or Early Discon Visit[e]
Follow-up (FU) Week No.																	FU2	FU4	FU6	FU8	FU10	FU18	FU26	FU34	
Visit Window			±2 days	±3 days													±4 days					±2 weeks			
Administrative Procedures																									
Informed Consent[f]	X																								
Informed Consent for Future Biomedical Research (optional)	X																								
Inclusion/Exclusion Criteria	X	X																							
Patient Identification Card	X																								
Medical History	X																								
Prior/Concomitant Medication Review[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Therapy Allocation/ Randomization		X																							
HSCT Details Review[h]		X																							
Study Medication Diary Review[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									X
Clinical Procedures/ Assessments																									
Physical Examination[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								X
Weight	X															X									X
Height	X																								

Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	Screen	Treatment (Week 1)		Treatment (Weeks 2 to 14[c])													Post-treatment Follow-up (Weeks 15 to 24[c])					Post-treatment Follow-up (Weeks 25 to 48[c])			
Week No. (unless otherwise indicated)	SCR[a]	Day 1[b]	Day 7	2	3	4	5	6	7	8	9	10[d]	11[d]	12[d]	13[d]	End of Study Therapy Visit 14[d]	16	18	20	22	24	32	40	48	CMV Infection or Early Discon Visit[e]
Follow-up (FU) Week No.																	FU2	FU4	FU6	FU8	FU10	FU18	FU26	FU34	
Visit Window			±2 days	±3 days													±4 days					±2 weeks			
Vital Signs (heart rate, blood pressure, respiratory rate, body temperature)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								X
12-Lead Electrocardiogram[l]	X			X												X									
Child-Pugh Score (see Appendix 12.5)	X																								
Patient Confirmation of Birth Control[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Adverse Events Monitoring[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/ Assessments[o]																									
Chemistry/ Hematology	X[p]	X		X		X				X				X		X	X								X
Urinalysis	X[p]	X														X									X
Serum β-Human Chorionic Gonadotropin (β-hCG) in women of childbearing potential	X																								
Urine Pregnancy Test in women of childbearing potential		X				X				X						X									X
Serum inhibin B,		X														X					X				X

Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	Screen	Treatment (Week 1)		Treatment (Weeks 2 to 14[c])													Post-treatment Follow-up (Weeks 15 to 24[c])					Post-treatment Follow-up (Weeks 25 to 48[c])			
Week No. (unless otherwise indicated)	SCR[a]	Day 1[b]	Day 7	2	3	4	5	6	7	8	9	10[d]	11[d]	12[d]	13[d]	End of Study Therapy Visit 14[d]	16	18	20	22	24	32	40	48	CMV Infection or Early Discon Visit[e]
Follow-up (FU) Week No.																	FU2	FU4	FU6	FU8	FU10	FU18	FU26	FU34	
Visit Window			±2 days	±3 days													±4 days					±2 weeks			
LH, FSH, testosterone levels in men																									
HIV/Hepatitis B, C Screen[q]	X																								
Blood for Genetics [r]		X																							
CMV Procedures/ Assessments																									
CMV DNA PCR[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMV Disease Assessment (see Appendix 12.4)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Outcomes Assessment[t]		X				X				X						X	X		X		X	X	X	X	X
Quality of Life Assessment[u]		X														X					X			X	X
CMV DNA Sequence Analysis[v]																									X
Pharmacokinetics																									
Population PK[w]		X	X	X		X		X		X		X		X		X									
Intensive PK[x]			X																						
Study Therapy Administration																									
Letermovir/ Placebo[y,z]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									

a. Patients may be screened during a period starting from 15 days prior to transplantation through 28 days post-transplant. Screening test results must be available within 5 days prior to the planned randomization date. Patients will have plasma samples tested for CMV viremia using the CMV DNA PCR assay (for initial screening purposes, results of the assay done at a local laboratory will be acceptable). After establishing absence of CMV viremia, patients will be tested once a week by the central laboratory using the CMV DNA PCR assay until randomization (Day 1). The following are to be assessed within 5 days prior to randomization: Child Pugh Score; serum AST, ALT, and total bilirubin; and creatinine clearance.

b. Start of study therapy is Day 1. On the day of randomization, eligibility for enrollment into the study should be confirmed (including confirmation that HSCT has taken place). At that time, patients should have **NO** documented CMV viremia, as confirmed by CMV DNA PCR assay at the central laboratory (the Roche COBAS® AmpliPrep/COBAS TaqMan® [CAP/CTM] assay) in a plasma sample collected within 5 days prior to randomization**. (NOTE: Evidence of CMV viremia as reported by the central lab will include reporting of test results as "detectable, not quantifiable" or "detected" with a numeric value provided.)** Creatinine clearance and liver function test results within 5 days prior to randomization should also be available and be within the range allowable in this study, as outlined in Section 5.1.3 (Patient Exclusion Criteria). Study therapy may begin as early as the day of transplant and no later than 28 days post-transplant. Study therapy will continue through Week 14 (~100 days) post-transplant. Day 1 procedures/assessments must be performed prior to first dose of study therapy.

c. Weeks correspond to the end of the numbered weeks after randomization, i.e., Week 2, 3, 4, etc. corresponds to Days 14, 21, 28 after randomization, respectively.

d. End of Study Therapy Visit may occur on Week 10, 11, 12, 13, or 14 depending on when study therapy was started during the 28-day post-transplant window. For example, if study therapy was started on the day of transplant, the End of Study Therapy Visit would be the Week 14 Visit (which corresponds to Week 14 post-transplant). If study therapy was started 28 days post-transplant, the End of Study Therapy Visit would be the Week 10 Visit (which corresponds to Week 14 post-transplant). Any per protocol procedure listed under the Week 14 Visit should be conducted at the true End of Study Therapy Visit (at Week 10, 11, 12, 13, or 14 post-transplant, depending on when study therapy was started).

e. The visit will be a CMV Infection Visit for all patients who discontinue study therapy due to clinically significant CMV infection defined as the occurrence of CMV disease or the initiation of PET, or for patients who are either diagnosed with CMV disease or require initiation of PET after study therapy completion during the follow-up period (through Week 24 post-transplant). The visit will be an Early Discontinuation Visit for those patients who are prematurely discontinued from the trial up to Week 24 post-transplant. All procedures should be performed at this visit **immediately prior to** the initiation of treatment of CMV diseases or initiation of PET (i.e., on the day anti-CMV therapy is initiated). Most important, a confirmatory plasma sample for CMV PCR testing at the central laboratory should be collected at this visit. In the event that the confirmatory result obtained on the day of PET initiation is **NOT** available (e.g., sample is lost or mishandled by the investigator site prior to shipment, or is inadequate upon receipt at the central laboratory), a subsequent sample must be obtained and sent to the central laboratory within 7 days after PET initiation (preferably within 48-72 hours). The patient will be considered to have met the primary efficacy endpoint if this confirmatory laboratory result is positive.

f. The informed consent must be obtained before any study-specific procedure is performed. It is acceptable that the date of obtaining informed consent is earlier than the day of performing screening procedures. However, once informed consent is obtained adverse event reporting must be conducted.

g. Includes review of consumption of grapefruit, Seville oranges or their respective juices, and other quinine-containing drinks or food. **Anti-CMV medications administered for treatment of CMV disease or for initiation of PET and all drug/biologic therapies used to prevent/treat GVHD should be recorded at every visit through Week 48 post- transplant.** Prior to Week 14 post-transplant all concomitant medications should be reviewed and documented. During the follow-up period (after Week 14 through Week 48 post- transplant), concomitant medication review is limited to the above and all antimicrobials (antibacterials, antifungals, antivirals), chemotherapy agents, and immunosuppressant agents.

h. To collect all relevant data at randomization (Day 1) related to the recent HSCT including details regarding the conditioning regimen used, the date and type of transplant, the source of stem cells, type of graft manipulation, presence of GVHD, and GVHD prophylaxis regimen (if any) used.

i. Study Medication Diary completion and review will begin once patient is discharged from the hospital.

j. After randomization (Day 1), the physical examination does not need to be performed at every visit; a targeted physical exam should be performed only if a patient has any complaints.

k. Vital signs include heart rate (sitting), blood pressure (sitting), respiratory rate, and body temperature (oral). Patients should be resting in a semi-recumbent position for at least 10 minutes prior to measurement of vital signs. After randomization (Day 1), vital signs should only be performed if targeted physical examination is performed.

l. All 12-Lead ECGs will be obtained after the patient has remained in a semi-recumbent position for 10 minutes.

m. Patient must use acceptable methods of contraception from the time of consent through 90 days after the last dose of study therapy.

n. Adverse event (AE) monitoring prior to randomization (Day 1) is limited to AEs resulting from protocol-related procedures or interventions, those resulting in death, and those resulting in a patient not being randomized. After initiating study therapy, all AEs should be collected from randomization (Day 1) through Follow-up Week 2 visit (i.e. through Week 16 post-transplant) in all patients. Thereafter, only drug-related serious adverse events (SAEs) and SAEs leading to death will be collected from week 16 through Week 48 post-transplant. Refer to Section 7.2 (Assessing and Recording Adverse Events) for further details. Safety monitoring of infusion-site adverse events should be performed by the evaluation of the site of infusion during and at the end of IV study therapy. Events should be entered on the AE electronic case report form. The trial site guidance for assessment and follow-up for infusion-site adverse events can be found in the Investigator Trial File Binder.

o. Refer to Section 7.1.3 (Laboratory Procedures/Assessments) for further details regarding the laboratory safety tests. Laboratory safety tests may be conducted within 3 days prior to a scheduled study visit and no later than the day of the scheduled study visit.

p. For screening purposes, values from the patient's chart for required chemistry, hematology, and urinalysis tests are acceptable. If not available, this testing may be performed by the central laboratory.

q. Perform /Hepatitis B, C Screen only if not previously documented within the last 90 days. If hepatitis C virus antibody is positive, RNA PCR results should be provided (or, if not available, RNA PCR testing will be performed by the central laboratory). HIV antibody test results documented at any time prior to randomization of the patient will be acceptable. A copy of the report must be available. If documentation of a previous HIV test is not available, the HIV antibody test must be conducted using the central laboratory.

r. This sample will be drawn for *SLCO1B1* (OATP1B1) genotyping and for planned genetic analysis of DNA and drug response. Data analysis will be limited to *SLCO1B1* (OATP1B1) genotyping if there is either a documented law or regulation prohibiting the planned genetic analysis of DNA and drug response, or if the IRB/IEC does not approve of the planned genetic analysis of DNA and drug response. Any leftover extracted DNA will be stored for future biomedical research if the patient signs the FBR consent.

s. For initial screening, results of CMV DNA PCR assay performed at a local laboratory will be acceptable to establish absence of CMV viremia. After the Screening Visit until randomization, CMV DNA PCR testing will be performed once a week by the central laboratory using the Roche CAP/CTM Assay. Thereafter, CMV DNA PCR testing will be performed by the central laboratory at every visit as specified in the Flow Chart. The CMV DNA PCR test may be conducted within 3 days prior to a scheduled study visit and no later than the day of the scheduled study visit. (This CMV DNA PCR testing window is not applicable to a CMV Infection Visit. See note below.) Plasma samples for CMV PCR testing at the central laboratory will also be collected at the CMV Infection or Early Discontinuation Visit. Note: It is mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory immediately prior to (i.e., on the day of) initiating treatment for CMV disease or PET in ALL instances. In the event that the confirmatory result obtained on the day of PET initiation is **NOT** available (e.g., sample is lost or mishandled by the investigator site prior to shipment, or is inadequate upon receipt at the central laboratory), a subsequent sample must be obtained and sent to the central laboratory within 7 days after PET initiation (preferably within 48-72 hours). Any results of local laboratory CMV PCR must also be reported. If the patient consents to the Future Biomedical Research sub-study, any leftover samples from CMV DNA PCR will be stored for future research.

t. To collect information such as all-cause mortality, re-hospitalizations, GVHD, opportunistic infections (e.g. systemic bacterial and invasive fungal infections), and engraftment.

u. The EuroQol (EQ)-5D and Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) questionnaires which are validated patient reported outcome tools will be used to measure quality of life.

v. CMV DNA Sequence Analysis to be performed only in patients with clinically significant CMV infection.

w. Population (sparse) PK samples will be collected in all patients. The 9 samples at the indicated visits will be collected 0 – 2 hours pre-dose. As treatment may range 10 – 14 weeks, the Week 12 and Week 14 visit samples may not be collected in all patients.

x Intensive PK sampling will be performed in a subset of ~100 patients. The 5 samples will be collected at the Day 7 visit at the following time points: pre-dose, 1 hour (± 10 min) following oral administration (or within less than 10 min **after** infusion completion, when given IV), 2.5 hours following oral/IV administration (± 30 min), 8 hours following oral/IV administration (range of 6-10 hours), and 24 hours following oral/IV administration (range of 22-24 hours; 0-2 hours prior to next day's dose). All identified patients who choose to participate in intensive PK sampling will sign an additional informed consent prior to the collection of samples.

y. Both oral (tablet) and intravenous (IV) formulation of letermovir (and placebo) will be available for study therapy. Patients will be initiated with the oral (tablet) formulation of study therapy provided they are able to swallow and do not have a condition (e.g., vomiting, diarrhea, or malabsorptive condition) that may interfere with the absorption of the tablets. For patients who cannot swallow and/or have a condition that may interfere with the absorption of the oral formulation, study therapy can be initiated with or switched to the IV formulation. The IV formulation should be switched to oral study therapy (i.e., at the next planned dose) as soon as such patients are able to swallow and/or the condition necessitating the use of the IV formulation resolves. Use of the IV formulation should generally be limited to 4 weeks or less in duration. However, it will be left to the investigator's discretion to continue IV administration beyond 4 weeks, if the benefit/risk ratio supports continued administration.

z. In this study, the dose of letermovir will change based on whether concomitant cyclosporine is received. The same dose of letermovir will be administered for both formulations. Patients in the letermovir treatment group will receive either 240 mg letermovir qd, if receiving concomitant cyclosporine, or 480 mg letermovir qd, if not on cyclosporine. If cyclosporine is initiated after starting study therapy, the next dose of letermovir (administered up to 24 hours later) should be decreased to 240 mg qd. If cyclosporine is discontinued permanently or for the long-term in a patient, the next dose of letermovir (administered up to 24 hours later) should be increased from 240 mg to 480 mg qd. If cyclosporine is temporarily held due to high levels detected by therapeutic blood monitoring, the dose of letermovir need not be adjusted. Corresponding changes in tablets for oral formulation with changes in cyclosporine dosing will also occur in the placebo group in an effort to maintain the study blind.

Table S2. Trial laboratory tests performed at the central laboratories.

Hematology[a]	Chemistry[a]	Urinalysis[a]	Other
Hematocrit	Albumin	Blood	Follicle Stimulating Hormone (FSH), luteinizing hormone (LH), testosterone and inhibin B levels in males
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)
Platelet count	Alanine aminotransferase (ALT)	Protein	Urine β-human chorionic gonadotropin (β-hCG)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Hepatitis B surface antigen (HBsAg)[b]
	Bicarbonate	Microscopic exam, if abnormal results are noted	Hepatitis C virus antibody (HCV-Ab)[b]
	Calcium		Hepatitis C RNA PCR[b]
	Chloride		HIV antibody (HIV-Ab)[b]
	Creatinine		CMV DNA PCR[c]
	Creatinine Clearance (screening only)		CMV DNA Sequence Analysis[d]
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin		
	Indirect Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
	Prothrombin time (PT) International normalized ratio (INR)		

[a] For screening, values from the patient's chart for required chemistry, hematology, and urinalysis tests are acceptable. If not available, this testing may be performed by the central laboratory.

[b] Hepatitis B, C testing only performed if results not previously documented within 90 days of screening. If hepatitis C virus antibody is positive, RNA PCR results should be provided (or, if not available, RNA PCR testing will be performed by the central laboratory). HIV antibody test results documented at any time prior to randomization of the patient will be acceptable. A copy of the report must be available. If documentation of a previous HIV test is not available, the HIV antibody test must be conducted using the central laboratory.

[c] For initial screening, results of CMV DNA PCR assay performed at a local laboratory will be acceptable to establish absence of CMV viremia. Thereafter, CMV DNA PCR testing will be performed by the central laboratory using the Roche CAP/CTM Assay.

[d] CMV DNA Sequence Analysis to be performed only in patients with detectable CMV DNA.

Table S3. Detailed baseline characteristics of randomized patients who received study drug, Safety Population

	Letermovir		Placebo	
	n	(%)	n	(%)
N	373	(100)	192	(100)
Male gender	211	(56.6)	116	(60.4)
Median age, years [range]	53	[18, 75]	54	[19, 78]
Race				
White	301	(80.7)	162	(84.4)
Asian	40	(10.7)	18	(9.4)
Black	8	(2.1)	4	(2.1)
Other	24	(6.4)	8	(4.2)
Hispanic or Latino Ethnicity	30	(8.0)	10	(5.2)
Median weight, kg [range]	76.2	[35.1, 141.5]	74.4	[40.9, 113.1]
Body mass index, kg/m^2 [range]	25.6	[17.0, 49.0]	25.1	[16.6, 49.0]
Donor CMV Seropositive	230	(61.7)	114	(59.4)
Primary reason for HCT				
Acute myeloid leukemia	142	(38.1)	72	(37.5)
Myelodysplastic syndrome	63	(16.9)	22	(11.5)
Non-Hodgkin lymphoma	47	(12.6)	28	(14.6)
Acute lymphocytic leukemia	35	(9.4)	17	(8.9)
Multiple myeloma	14	(3.8)	10	(5.2)
Chronic myeloid leukemia	17	(4.6)	6	(3.1)
Aplastic anemia	9	(2.4)	11	(5.7)
Myelofibrosis	9	(2.4)	6	(3.1)
Chronic lymphocytic leukemia	10	(2.7)	4	(2.1)
Other diseases	27	(7.2)	16	(8.3)
HLA matching and donor type				
Matched unrelated	138	(37.0)	78	(40.6)
Matched related	121	(32.4)	63	(32.8)
Mismatched related	63	(16.9)	24	(12.5)
Mismatched unrelated	51	(13.7)	27	(14.1)
Haploidentical related donor	60	(16.1)	21	(10.9)
Stem cell source				
Peripheral blood	279	(74.8)	134	(69.8)
Bone marrow	82	(22.0)	47	(24.5)
Cord blood	12	(3.2)	11	(5.7)

	Letermovir		Placebo	
	n	(%)	n	(%)
Conditioning regimen[3]				
Myeloablative	186	(49.9)	97	(50.5)
Reduced intensity	92	(24.7)	54	(28.1)
Non-myeloablative	95	(25.5)	41	(21.4)
Antithymocyte globulin use	140	(37.5)	58	(30.2)
Alemtuzumab use	12	(3.2)	11	(5.7)
Ex vivo T-cell depletion[†]	9	(2.4)	5	(2.6)
Immunosuppressant use				
Cyclosporine	193	(51.7)	100	(52.1)
Tacrolimus	160	(42.9)	79	(41.1)
Mycophenolate[#]	120	(32.2)	51	(26.6)
Sirolimus	26	(7.0)	18	(9.4)
Everolimus	4	(1.1)	2	(1.0)
Median time to randomization, days after transplant [range]	9	[0, 28]	9	[0, 28]
Engraftment at randomization	132	(35.4)	74	(38.5)
Acute GVHD grade ≥2 at randomization	2	(0.8)	1	(0.5)
CMV DNA detected at randomization	48	(12.9)	22	(11.5)
CMV disease risk (randomization strata)				
High Risk*	121	(32.4)	54	(28.1)
Low Risk**	252	(67.6)	138	(71.9)

[†]Includes the *ex vivo* use of alemtuzumab

[#]Mycophenolate includes mycophenolate mofetil, mycophenolate sodium and mycophenolic acid.

[*]High risk: Patients meeting one or more of the following criteria at the time of randomization:

1. Related donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR
2. Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1
3. Haploidentical donor
4. Use of umbilical cord blood as stem cell source
5. Use of ex vivo T-cell-depleted grafts
6. Grade 2 or greater graft-versus-host disease (GVHD), requiring the use of >1 mg/kg/day of prednisone or equivalent

[**]Low risk: All patients not meeting definition of high risk.

Table S4. Pharmacokinetic model-based predicted letermovir AUC_{24} for patients who participated in the trial, according to letermovir dose, route of administration, cyclosporine exposure, and Asian descent.

Subgroup	Median letermovir AUC_{24} (ng·h/mL)	90% prediction interval
Cyclosporine, 240mg IV, Asian	71490	47420-108200
Cyclosporine, 240mg IV, Non-Asian	70260	46230-106100
Cyclosporine, 240mg Oral, Asian	61560	29230-126200
Cyclosporine, 240mg Oral, Non-Asian	60770	28720-121900
No Cyclosporine, 480mg IV, Asian	99680	64500-145000
No Cyclosporine, 480mg IV, Non-Asian	99950	65320-147800
No Cyclosporine, 480mg Oral, Asian	33850	15830-69950
No Cyclosporine, 480mg Oral, Non-Asian	34430	16900-73660

AUC_{24}, area under the concentration vs time curve 0 to 24 hours post-dose at steady-state

The non-linear mixed effects model was based on 2888 measured letermovir concentration results from patients who participated in three phase 1 (n=36), one phase 2 (n=36), and the phase 3 trial (n=350) who had measurements at least a week into treatment for steady-state assessments. The data included samples from patients who had intense and sparse pharmacokinetic measurements.
The final phase 3 structural model used here was a 2-compartment model with linear elimination and absorption, including a lag of absorption. Study patients were found to have lower bioavailability and slower absorption than healthy volunteers. Letermovir bioavailability was approximately 85% when co-administered with cyclosporine and about 35% when ingested without concomitant cyclosporine use.

Table S5. Pharmacokinetic model-based predicted letermovir minimum concentrations (Cmin) for patients who participated in the trial, according to letermovir dose, route of administration, cyclosporine exposure, and Asian descent.

Subgroup	Median letermovir Cmin (ng·h/mL)	90% prediction interval
Cyclosporine, 240mg IV, Asian	684.2	217.9-1635
Cyclosporine, 240mg IV, Non-Asian	774.3	302-1689
Cyclosporine, 240mg Oral, Asian	1200	346.9-3154
Cyclosporine, 240mg Oral, Non-Asian	1201	393.3-3133
No Cyclosporine, 480mg IV, Asian	607.7	155.5-1482
No Cyclosporine, 480mg IV, Non-Asian	767.6	295.9-1754
No Cyclosporine, 480mg Oral, Asian	506.4	118.4-1628
No Cyclosporine, 480mg Oral, Non-Asian	539.2	151.9-1552

Table S6. Reasons for discontinuation from study from randomization through end of treatment (Week 14 post-HCT).

	Letermovir		Placebo	
	n	(%)	n	(%)
Patients	376		194	
Randomized but not treated	3	(0.8)	2	(1.0)
Completed	267	(71.0)	80	(41.2)
Discontinued	106	(28.2)	112	(57.7)
Clinically significant CMV infection (endpoint)	24	(6.4)	82	(42.3)
Adverse event	42	(11.2)	19	(9.8)
Withdrawal by patient§	20	(5.3)	4	(2.1)
Physician decision	7	(1.9)	2	(1.0)
Death	5	(1.3)	4	(2.1)
Non-compliance with study drug	5	(1.3)	1	(0.5)
Excluded medication*	3	(0.8)	0	(0.0)

§ For letermovir-treated patients (n=20), documented reasons for withdrawal were: no reason given in 6, pill burden in 3, underlying disease relapse in 2, unable or unwilling to return for on-site study visits in 2, graft-versus-host disease in 2, and 1 each due to nausea, diarrhea, tremor and gait disturbance, study blood draw volume, and feeling overwhelmed. For placebo-treated patients (n=4), the reasons were one each for fatigue, pill burden, unwillingness to return for on-site study visits, and feeling overwhelmed.

* These patients were discontinued from study medication as they needed concomitant prohibited medications.

Table S7. Summary of patients with CMV viremia through Week 14 Post-HCT, with and without clinically significant CMV infection, Primary Efficacy Population.

	Letermovir (N=325)		Placebo (N=170)	
	n	% (95% CI)	n	% (95% CI)
All patients with viremia†	103	31.7 (26.7, 37.1)	118	69.4 (61.9, 76.2)
Maximum CMV DNA (copies/mL) in subjects with clinically significant CMV infection (N=92)				
Patients with data	25		67	
Median	233		1014	
Range	150 to 27946		150 to 106830	
(Q1, Q3)	(150, 424)		(213, 3864)	
detected but not quantifiable	9	2.8 (1.3, 5.2)	13	7.6 (4.1, 12.7)
quantifiable and <1000	12	3.7 (1.9, 6.4)	20	11.8 (7.3, 17.6)
≥1000 and <10000	3	0.9 (0.2, 2.7)	25	14.7 (9.7, 20.9)
≥10000	1	0.3 (0.0, 1.7)	9	5.3 (2.4, 9.8)
Maximum CMV DNA (copies/mL) in subjects without clinically significant CMV infection (N=129)				
Patients with data	78		51	
Median	150		150	
Range	150 to 2398		150 to 7857	
(Q1, Q3)	(150, 150)		(150, 150)	
detected but not quantifiable	71	21.8 (17.5, 26.7)	39	22.9 (16.9, 30.0)
quantifiable and <1000	6	1.8 (0.7, 4.0)	8	4.7 (2.1, 9.1)
≥1000 and <10000	1	0.3 (0.0, 1.7)	4	2.4 (0.6, 5.9)
≥10000	0	0.0 (0.0, 1.1)	0	0.0 (0.0, 2.1)

† Viremia refers to detectable plasma CMV DNA by PCR testing using the central laboratory. N = number of evaluable patients in in each treatment group.

n = Number of patients in each sub-category.

% = Percent of patients in each sub-category.

Q1=25th percentile; Q3=75th percentile; CI=Confidence Interval.

Patients with detectable, non-quantifiable CMV VL (<151 copies/mL), a value of 150 copies/mL was imputed.

One IU/mL of CMV DNA is approximately 1.1 copies/mL in this assay.

Table S8. Summary of patients with CMV viremia through Week 24 Post-HCT, with and without clinically significant CMV infection, Primary Efficacy Population.

	Letermovir (N=325)		Placebo (N=170)	
	n	% (95% CI)	n	% (95% CI)
All patients with CMV viremia†	186	57.2 (51.7, 62.7)	124	72.9 (65.6, 79.5)
Maximum CMV DNA (copies/mL) in patients with clinically significant CMV infection (N=128)				
Patients with data	57		71	
Median	405		1014	
Range	150 to 54654		150 to 106830	
(Q1, Q3)	(150, 1299)		(221, 3653)	
detected, not quantifiable	15	4.6 (2.6, 7.5)	13	7.6 (4.1, 12.7)
quantifiable and <1000	23	7.1 (4.5, 10.4)	22	12.9 (8.3, 18.9)
≥1000 and <10000	11	3.4 (1.7, 6.0)	27	15.9 (10.7, 22.3)
≥10000	8	2.5 (1.1, 4.8)	9	5.3 (2.4, 9.8)
Maximum CMV DNA (copies/mL) in patients without clinically significant CMV infection (N=182)				
Patients with data	129		53	
Median	150		150	
Range	150 to 2398		150 to 7857	
(Q1, Q3)	(150, 150)		(150, 150)	
detected, not quantifiable	101	31.1 (26.1, 36.4)	40	23.5 (17.4, 30.6)
quantifiable and <1000	21	6.5 (4.0, 9.7)	9	5.3 (2.4, 9.8)
≥1000 and <10000	7	2.2 (0.9, 4.4)	4	2.4 (0.6, 5.9)
≥10000	0	0.0 (0.0, 1.1)	0	0.0 (0.0, 2.1)

† Viremia refers to detectable plasma CMV DNA by PCR testing using the central laboratories. N = number of evaluable patients in in each treatment group.

n = Number of patients in each sub-category.

% = Percent of patients in each sub-category.

Q1=25th percentile; Q3=75th percentile; CI=Confidence Interval.

Patients with detectable, non-quantifiable CMV VL (<151 copies/mL), a value of 150 copies/mL was imputed.

One IU/mL of CMV DNA is approximately 1.1 copies/mL in this assay.

Table S9. Summary of initial antivirals use for cytomegalovirus preemptive treatment (PET) through Week 24 post-HCT, Primary Efficacy Population.

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population who started PET	**52**		**68**		**120**	
Antivirals Used for PET Initiation†	**52**	**(100.0)**	**68**	**(100.0)**	**120**	**(100.0)**
Valganciclovir	28	(53.8)	34	(50.0)	62	(51.7)
Ganciclovir	18	(34.6)	29	(42.6)	47	(39.2)
Foscarnet	8	(15.4)	5	(7.4)	13	(10.8)
Cidofovir	0	(0.0)	0	(0.0)	0	(0.0)
Patients with antiviral combination Used for PET initiation	**10**	**(19.2)**	**10**	**(14.7)**	**20**	**(16.7)**
Patients with Antiviral Changed During PET	**4**	**(7.7)**	**3**	**(4.4)**	**7**	**(5.8)**
Duration of Treatment (Days)‡						
Patients with data						
N	52		68		120	
Median	29		36		35.5	
Q1, Q3	17.5, 78.5		24.5, 63.5		22, 66	
Range	3 to 334		5 to 300		3 to 334	
Viral Clearance in Patients Where PET Initiated§						
Confirmed	40	(76.9)	50	(73.5)	90	(75.0)
Not confirmed	12	23.1	18	26.5	30	25.0
Discontinued early from study	8	15.4	16	23.5	24	20.0
Viral Clearance Not Achieved	4	7.7	2	2.9	6	5.0

† Every subject is counted a single time for each applicable specific medication.

‡ Duration is determined from start date of first dose to the last date of the antiviral used for the first episode of PET.

§ Viral clearance is defined as 2 consecutive undetectable viral loads (by central laboratory) after PET initiation.

n (%) = Number (percent) of patients in each sub-category; Q1=25th percentile; Q3=75th percentile.

Table S10. Adverse event summary through Week 24 post-HCT, Safety Population.

	Letermovir		Placebo	
	n	(%)	n	(%)
Patients	373		192	
with one or more adverse events	366	(98.1)	192	(100.0)
with drug-related† adverse events	63	(16.9)	23	(12.0)
with non-serious adverse events	364	(97.6)	190	(99.0)
with serious adverse events	193	(51.7)	109	(56.8)
with serious drug-related† adverse events	3	(0.8)	3	(1.6)
who died	61	(16.4)	38	(19.8)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	72	(19.3)	98	(51.0)
discontinued due to a drug-related adverse event	18	(4.8)	7	(3.6)
discontinued due to a serious adverse event	35	(9.4)	27	(14.1)
discontinued due to a serious drug-related adverse event	3	(0.8)	3	(1.6)

†Determined by the investigator to be related to the drug.

‡Study medication withdrawn.

n = Number of patients randomized and treated in each treatment group.

Table S11. Analysis of patients with adverse events during the trial's treatment phase in the Safety Population, by system organ class* and preferred terms.

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Patients	373		192		
with one or more adverse events	365	(97.9)	192	(100.0)	-2.1 (-4.2, -0.2)
Blood and lymphatic system disorders	**98**	**(26.3)**	**51**	**(26.6)**	**-0.3 (-8.2, 7.2)**
Anemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Eosinophilia	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Febrile neutropenia	31	(8.3)	18	(9.4)	-1.1 (-6.6, 3.6)
Leukopenia	11	(2.9)	7	(3.6)	-0.7 (-4.6, 2.2)
Neutropenia	14	(3.8)	7	(3.6)	0.1 (-3.9, 3.2)
Pancytopenia	7	(1.9)	6	(3.1)	-1.2 (-4.9, 1.3)
Thrombocytopenia	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Cardiac disorders	**47**	**(12.6)**	**12**	**(6.3)**	**6.4 (1.1, 11.0)**
Atrial fibrillation	13	(3.5)	2	(1.0)	2.4 (-0.5, 5.0)
Atrial flutter	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Cardiac failure	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Sinus tachycardia	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Tachycardia	15	(4.0)	4	(2.1)	1.9 (-1.5, 4.8)
Ear and labyrinth disorders	**17**	**(4.6)**	**2**	**(1.0)**	**3.5 (0.5, 6.3)**
Ear pain	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Vertigo	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Eye disorders	**62**	**(16.6)**	**32**	**(16.7)**	**-0.0 (-6.9, 6.2)**
Blepharitis	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Conjunctival hemorrhage	7	(1.9)	0	(0.0)	1.9 (-0.1, 3.8)
Dry eye	22	(5.9)	10	(5.2)	0.7 (-3.9, 4.5)
Lacrimation increased	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Vision blurred	11	(2.9)	1	(0.5)	2.4 (-0.1, 4.8)
Gastrointestinal disorders	**261**	**(70.0)**	**129**	**(67.2)**	**2.8 (-5.1, 11.0)**
Abdominal discomfort	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Abdominal distension	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Abdominal pain	44	(11.8)	18	(9.4)	2.4 (-3.3, 7.5)
Abdominal pain upper	15	(4.0)	16	(8.3)	-4.3 (-9.4, -0.3)
Angina bullosa hemorrhagica	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Aphthous ulcer	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Constipation	27	(7.2)	20	(10.4)	-3.2 (-8.8, 1.5)
Diarrhea	97	(26.0)	47	(24.5)	1.5 (-6.3, 8.8)
Dry mouth	20	(5.4)	6	(3.1)	2.2 (-1.7, 5.6)
Dyspepsia	20	(5.4)	7	(3.6)	1.7 (-2.4, 5.1)
Dysphagia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Gastrointestinal disorders	**261**	**(70.0)**	**129**	**(67.2)**	**2.8 (-5.1, 11.0)**
Flatulence	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Gastritis	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Gastroesophageal reflux disease	4	(1.1)	9	(4.7)	-3.6 (-7.7, -1.0)
Hematochezia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Hemorrhoids	18	(4.8)	4	(2.1)	2.7 (-0.8, 5.8)
Nausea	99	(26.5)	45	(23.4)	3.1 (-4.6, 10.3)
Proctalgia	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Stomatitis	23	(6.2)	9	(4.7)	1.5 (-3.0, 5.2)
Tongue coated	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Toothache	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Vomiting	69	(18.5)	26	(13.5)	5.0 (-1.7, 11.0)
General disorders and administration site conditions	**211**	**(56.6)**	**100**	**(52.1)**	**4.5 (-4.2, 13.1)**
Asthenia	23	(6.2)	7	(3.6)	2.5 (-1.6, 6.1)
Chest pain	16	(4.3)	5	(2.6)	1.7 (-2.0, 4.7)
Chills	14	(3.8)	4	(2.1)	1.7 (-1.8, 4.5)
Face edema	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Fatigue	50	(13.4)	21	(10.9)	2.5 (-3.6, 7.8)
Malaise	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Mucosal inflammation	46	(12.3)	24	(12.5)	-0.2 (-6.4, 5.3)
Edema	12	(3.2)	2	(1.0)	2.2 (-0.7, 4.7)
Edema peripheral	54	(14.5)	18	(9.4)	5.1 (-0.8, 10.4)
Pain	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Peripheral swelling	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Fever	77	(20.6)	43	(22.4)	-1.8 (-9.2, 5.2)
Hepatobiliary disorders	**22**	**(5.9)**	**15**	**(7.8)**	**-1.9 (-7.0, 2.3)**
Hepatic function abnormal	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Hyperbilirubinemia	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Immune system disorders	**153**	**(41.0)**	**80**	**(41.7)**	**-0.6 (-9.3, 7.8)**
Drug hypersensitivity	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Graft-versus-host disease	146	(39.1)	74	(38.5)	0.6 (-8.0, 8.9)
Hypogammaglobulinemia	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Infections and infestations	**241**	**(64.6)**	**139**	**(72.4)**	**-7.8 (-15.5, 0.4)**
Bacteremia	20	(5.4)	4	(2.1)	3.3 (-0.3, 6.4)
Bronchopulmonary aspergillosis	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Candida infection	11	(2.9)	4	(2.1)	0.9 (-2.5, 3.5)
Clostridium difficile colitis	9	(2.4)	4	(2.1)	0.3 (-3.0, 2.8)
Conjunctivitis	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Infections and infestations	**241**	**(64.6)**	**139**	**(72.4)**	**-7.8 (-15.5, 0.4)**
Cystitis	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Cytomegalovirus infection	31	(8.3)	88	(45.8)	-37.5 (-45.1, -30.0)
Device related infection	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Epstein-Barr virus infection	14	(3.8)	6	(3.1)	0.6 (-3.2, 3.6)
Folliculitis	13	(3.5)	4	(2.1)	1.4 (-2.0, 4.2)
Herpes zoster	6	(1.6)	0	(0.0)	1.6 (-0.4, 3.5)
Human herpesvirus 6 infection	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Nasopharyngitis	15	(4.0)	4	(2.1)	1.9 (-1.5, 4.8)
Oral candidiasis	12	(3.2)	2	(1.0)	2.2 (-0.7, 4.7)
Oral herpes	7	(1.9)	4	(2.1)	-0.2 (-3.5, 2.1)
Pharyngitis	8	(2.1)	6	(3.1)	-1.0 (-4.7, 1.7)
Pneumonia	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Respiratory tract infection	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Rhinitis	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Rhinovirus infection	10	(2.7)	2	(1.0)	1.6 (-1.2, 4.0)
Sepsis	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Septic shock	4	(1.1)	5	(2.6)	-1.5 (-5.0, 0.6)
Sinusitis	7	(1.9)	2	(1.0)	0.8 (-2.0, 3.0)
Staphylococcal bacteremia	10	(2.7)	6	(3.1)	-0.4 (-4.2, 2.3)
Upper respiratory tract infection	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Urinary tract infection	16	(4.3)	6	(3.1)	1.2 (-2.7, 4.3)
Urinary tract infection bacterial	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Viremia	11	(2.9)	11	(5.7)	-2.8 (-7.2, 0.6)
Injury, poisoning and procedural complications	**42**	**(11.3)**	**27**	**(14.1)**	**-2.8 (-9.1, 2.8)**
Contusion	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Fall	3	(0.8)	4	(2.1)	-1.3 (-4.5, 0.7)
Skin abrasion	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Investigations	**133**	**(35.7)**	**60**	**(31.3)**	**4.4 (-3.9, 12.4)**
Alanine aminotransferase increased	24	(6.4)	16	(8.3)	-1.9 (-7.1, 2.4)
Aspartate aminotransferase increased	19	(5.1)	13	(6.8)	-1.7 (-6.5, 2.2)
Blood albumin decreased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Blood alkaline phosphatase increased	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Blood bilirubin increased	9	(2.4)	5	(2.6)	-0.2 (-3.7, 2.4)
Blood creatinine increased	36	(9.7)	13	(6.8)	2.9 (-2.3, 7.4)
Blood glucose increased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Blood potassium increased	7	(1.9)	1	(0.5)	1.4 (-1.1, 3.4)
Blood testosterone decreased	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Blood urea increased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
C-reactive protein increased	11	(2.9)	1	(0.5)	2.4 (-0.1, 4.8)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Investigations	**133**	**(35.7)**	**60**	**(31.3)**	**4.4 (-3.9, 12.4)**
Carbon dioxide decreased	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Electrocardiogram QT prolonged	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Gamma-glutamyltransferase increased	3	(0.8)	4	(2.1)	-1.3 (-4.5, 0.7)
Hematocrit decreased	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Hemoglobin decreased	6	(1.6)	0	(0.0)	1.6 (-0.4, 3.5)
International normalized ratio increased	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Lymphocyte count decreased	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Neutrophil count decreased	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Platelet count decreased	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Weight decreased	15	(4.0)	7	(3.6)	0.4 (-3.6, 3.5)
Weight increased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
White blood cell count decreased	8	(2.1)	2	(1.0)	1.1 (-1.7, 3.3)
Metabolism and nutrition disorders	**134**	**(35.9)**	**63**	**(32.8)**	**3.1 (-5.3, 11.2)**
Decreased appetite	38	(10.2)	22	(11.5)	-1.3 (-7.2, 3.9)
Dehydration	2	(0.5)	5	(2.6)	-2.1 (-5.5, -0.1)
Diabetes mellitus	6	(1.6)	5	(2.6)	-1.0 (-4.5, 1.4)
Fluid overload	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Gout	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Hyperglycemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Hyperkalemia	27	(7.2)	4	(2.1)	5.2 (1.4, 8.6)
Hypernatremia	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Hypertriglyceridemia	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Hyperuricemia	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Hypoalbuminemia	10	(2.7)	7	(3.6)	-1.0 (-4.9, 1.9)
Hypocalcaemia	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Hypokalemia	22	(5.9)	11	(5.7)	0.2 (-4.5, 4.0)
Hypomagnesaemia	23	(6.2)	15	(7.8)	-1.6 (-6.8, 2.6)
Hyponatremia	21	(5.6)	10	(5.2)	0.4 (-4.1, 4.1)
Hypophosphatemia	5	(1.3)	5	(2.6)	-1.3 (-4.7, 1.0)
Vitamin D deficiency	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Musculoskeletal and connective tissue disorders	**121**	**(32.4)**	**57**	**(29.7)**	**2.8 (-5.5, 10.6)**
Arthralgia	26	(7.0)	10	(5.2)	1.8 (-2.9, 5.7)
Back pain	23	(6.2)	14	(7.3)	-1.1 (-6.1, 3.0)
Bone pain	14	(3.8)	5	(2.6)	1.1 (-2.5, 4.1)
Muscle spasms	12	(3.2)	7	(3.6)	-0.4 (-4.4, 2.6)
Muscular weakness	6	(1.6)	3	(1.6)	0.0 (-3.0, 2.2)
Musculoskeletal chest pain	7	(1.9)	1	(0.5)	1.4 (-1.1, 3.4)
Musculoskeletal pain	15	(4.0)	3	(1.6)	2.5 (-0.8, 5.2)
Myalgia	19	(5.1)	3	(1.6)	3.5 (0.2, 6.5)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Musculoskeletal and connective tissue disorders	**121**	**(32.4)**	**57**	**(29.7)**	**2.8 (-5.5, 10.6)**
Myopathy	2	(0.5)	5	(2.6)	-2.1 (-5.5, -0.1)
Neck pain	6	(1.6)	3	(1.6)	0.0 (-3.0, 2.2)
Pain in extremity	19	(5.1)	11	(5.7)	-0.6 (-5.2, 3.1)
Tendonitis	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**39**	**(10.5)**	**17**	**(8.9)**	**1.6 (-4.0, 6.5)**
Acute myeloid leukemia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Acute myeloid leukemia recurrent	11	(2.9)	8	(4.2)	-1.2 (-5.3, 1.8)
Nervous system disorders	**137**	**(36.7)**	**64**	**(33.3)**	**3.4 (-5.0, 11.5)**
Dizziness	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Dysgeusia	17	(4.6)	7	(3.6)	0.9 (-3.1, 4.2)
Headache	52	(13.9)	18	(9.4)	4.6 (-1.3, 9.8)
Hypoesthesia	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Neuropathy peripheral	8	(2.1)	6	(3.1)	-1.0 (-4.7, 1.7)
Paresthesia	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Presyncope	1	(0.3)	4	(2.1)	-1.8 (-5.0, -0.2)
Tremor	27	(7.2)	8	(4.2)	3.1 (-1.3, 6.9)
Psychiatric disorders	**78**	**(20.9)**	**30**	**(15.6)**	**5.3 (-1.6, 11.6)**
Anxiety	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Confusional state	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Delirium	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Depression	11	(2.9)	3	(1.6)	1.4 (-1.8, 3.9)
Insomnia	34	(9.1)	10	(5.2)	3.9 (-0.9, 8.1)
Mental status changes	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Renal and urinary disorders	**81**	**(21.7)**	**46**	**(24.0)**	**-2.2 (-9.8, 4.9)**
Acute kidney injury	36	(9.7)	25	(13.0)	-3.4 (-9.5, 1.9)
Cystitis hemorrhagic	4	(1.1)	6	(3.1)	-2.1 (-5.7, 0.2)
Dysuria	11	(2.9)	6	(3.1)	-0.2 (-3.9, 2.7)
Hematuria	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Nocturia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Pollakiuria	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Renal failure	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Renal impairment	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Urinary retention	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Respiratory, thoracic and mediastinal disorders	**147**	**(39.4)**	**71**	**(37.0)**	**2.4 (-6.1, 10.7)**
Cough	53	(14.2)	20	(10.4)	3.8 (-2.2, 9.2)
Dyspnea	30	(8.0)	6	(3.1)	4.9 (0.8, 8.6)
Dyspnea exertional	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Epistaxis	23	(6.2)	11	(5.7)	0.4 (-4.3, 4.3)
Hemoptysis	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Hypoxia	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Nasal congestion	8	(2.1)	1	(0.5)	1.6 (-0.9, 3.7)
Oropharyngeal pain	28	(7.5)	15	(7.8)	-0.3 (-5.5, 4.1)
Pleural effusion	10	(2.7)	3	(1.6)	1.1 (-2.0, 3.6)
Productive cough	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Pulmonary edema	6	(1.6)	4	(2.1)	-0.5 (-3.8, 1.8)
Respiratory failure	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Rhinorrhea	12	(3.2)	9	(4.7)	-1.5 (-5.7, 1.7)
Upper-airway cough syndrome	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Skin and subcutaneous tissue disorders	**179**	**(48.0)**	**80**	**(41.7)**	**6.3 (-2.4, 14.8)**
Dermatitis contact	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Dry skin	26	(7.0)	8	(4.2)	2.8 (-1.6, 6.6)
Erythema	33	(8.8)	11	(5.7)	3.1 (-1.8, 7.4)
Night sweats	7	(1.9)	2	(1.0)	0.8 (-2.0, 3.0)
Petechiae	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Pruritus	26	(7.0)	11	(5.7)	1.2 (-3.5, 5.2)
Rash	76	(20.4)	41	(21.4)	-1.0 (-8.4, 5.9)
Rash erythematous	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Rash maculo-papular	7	(1.9)	4	(2.1)	-0.2 (-3.5, 2.1)
Rash pruritic	8	(2.1)	2	(1.0)	1.1 (-1.7, 3.3)
Skin exfoliation	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Skin hyperpigmentation	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Skin lesion	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Swelling face	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Vascular disorders	**69**	**(18.5)**	**40**	**(20.8)**	**-2.3 (-9.6, 4.4)**
Hematoma	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Hypertension	31	(8.3)	21	(10.9)	-2.6 (-8.4, 2.3)
Hypotension	14	(3.8)	9	(4.7)	-0.9 (-5.2, 2.4)
Orthostatic hypotension	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Venoocclusive disease	**7**	**(1.9)**	**3**	**(1.6)**	**0.3 (-2.8, 2.6)**

*System organ class groups are presented in bold, preferred adverse terms in regular font. Venooclussive disease includes events entered under either liver or vascular disorders.

† Based on Miettinen & Nurminen method. Every patient is counted a single time for each applicable row and column. A system organ class or specific adverse event appears on this report only if its incidence in one or both treatment groups was ≥ 4.

Table S12. Analysis of patients with serious adverse events through Week 24 post-HCT in the Safety Population, by system organ class* and preferred terms.

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Patients in population	373		192		
with one or more serious adverse events	193	(51.7)	109	(56.8)	-5.0 (-13.6, 3.7)
Blood and lymphatic system disorders	**18**	**(4.8)**	**6**	**(3.1)**	**1.7 (-2.2, 4.9)**
Febrile neutropenia	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Thrombocytopenia	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Gastrointestinal disorders	**17**	**(4.6)**	**7**	**(3.6)**	**0.9 (-3.1, 4.2)**
Diarrhoea	3	(0.8)	5	(2.6)	-1.8 (-5.2, 0.3)
General disorders and administration site conditions	**16**	**(4.3)**	**10**	**(5.2)**	**-0.9 (-5.4, 2.6)**
Multiple organ dysfunction syndrome	1	(0.3)	4	(2.1)	-1.8 (-5.0, -0.2)
Pyrexia	9	(2.4)	4	(2.1)	0.3 (-3.0, 2.8)
Hepatobiliary disorders	**5**	**(1.3)**	**4**	**(2.1)**	**-0.7 (-4.0, 1.4)**
Immune system disorders	**44**	**(11.8)**	**31**	**(16.1)**	**-4.3 (-10.9, 1.5)**
Graft versus host disease	43	(11.5)	29	(15.1)	-3.6 (-10.0, 2.1)
Infections and infestations	**93**	**(24.9)**	**47**	**(24.5)**	**0.5 (-7.3, 7.7)**
Bronchopulmonary aspergillosis	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Cytomegalovirus infection	13	(3.5)	14	(7.3)	-3.8 (-8.6, -0.1)
Pneumonia	14	(3.8)	4	(2.1)	1.7 (-1.8, 4.5)
Sepsis	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Septic shock	5	(1.3)	6	(3.1)	-1.8 (-5.4, 0.6)
Sinusitis	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Urinary tract infection	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Injury, poisoning and procedural complications	**8**	**(2.1)**	**9**	**(4.7)**	**-2.5 (-6.7, 0.4)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**48**	**(12.9)**	**28**	**(14.6)**	**-1.7 (-8.2, 4.0)**
Acute lymphocytic leukaemia recurrent	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Acute myeloid leukaemia	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Acute myeloid leukaemia recurrent	20	(5.4)	14	(7.3)	-1.9 (-6.9, 2.1)
Renal and urinary disorders	**13**	**(3.5)**	**14**	**(7.3)**	**-3.8 (-8.6, -0.1)**
Acute kidney injury	7	(1.9)	9	(4.7)	-2.8 (-6.9, 0.1)

	Letermovir n (%)	Placebo n (%)	Difference in % vs Placebo Estimate (95% CI)†
Respiratory, thoracic and mediastinal disorders	**12 (3.2)**	**8 (4.2)**	**-0.9 (-5.0, 2.2)**
Respiratory failure	4 (1.1)	0 (0.0)	1.1 (-0.9, 2.7)
Venoocclusive disease	**5 (1.3)**	**3 (1.6)**	-0.2 (-3.3, 1.8)

*System organ class groups are presented in bold, preferred adverse terms in regular font. Venooclussive disease includes events entered under either liver or vascular disorders.

† Based on Miettinen & Nurminen method. Every patient is counted a single time for each applicable row and column. A system organ class or specific adverse event appears on this report only if its incidence in one or both treatment groups was ≥ 4.

Table S13. Patients with laboratory findings that met predetermined criteria of worsening grade during trial treatment phase, Safety Population

Criterion†	Letermovir n/m (%)	Placebo n/m (%)	Total n/m (%)
CHEMISTRY			
Alanine Aminotransferase (IU/L)			
Grade 1: 1.25 - <2.5 x ULN	42/371 (11.3)	23/191 (12.0)	65/562 (11.6)
Grade 2: 2.5 - <5.0 x ULN	14/371 (3.8)	16/191 (8.4)	30/562 (5.3)
Grade 3: 5.0 - <10.0 x ULN	7/371 (1.9)	3/191 (1.6)	10/562 (1.8)
Grade 4: ≥10.0 x ULN	6/371 (1.6)	0/191 (0.0)	6/562 (1.1)
Aspartate Aminotransferase (IU/L)			
Grade 1: 1.25 - <2.5 x ULN	31/371 (8.4)	26/191 (13.6)	57/562 (10.1)
Grade 2: 2.5 - <5.0 x ULN	11/371 (3.0)	9/191 (4.7)	20/562 (3.6)
Grade 3: 5.0 - <10.0 x ULN	6/371 (1.6)	2/191 (1.0)	8/562 (1.4)
Grade 4: ≥10.0 x ULN	2/371 (0.5)	0/191 (0.0)	2/562 (0.4)
Alkaline Phosphatase (IU/L)			
Grade 1: 1.25 - <2.5 x ULN	37/371 (10.0)	15/191 (7.9)	52/562 (9.3)
Grade 2: 2.5 - <5.0 x ULN	10/371 (2.7)	8/191 (4.2)	18/562 (3.2)
Grade 3: 5.0 - <10.0 x ULN	2/371 (0.5)	0/191 (0.0)	2/562 (0.4)
Grade 4: ≥10.0 x ULN	0/371 (0.0)	0/191 (0.0)	0/562 (0.0)
Total Bilirubin (mg/dL)			
Grade 1: 1.1 - <1.6 x ULN	19/371 (5.1)	9/191 (4.7)	28/562 (5.0)
Grade 2: 1.6 - <2.6 x ULN	10/371 (2.7)	3/191 (1.6)	13/562 (2.3)
Grade 3: 2.6 - <5.0 x ULN	4/371 (1.1)	4/191 (2.1)	8/562 (1.4)
Grade 4: ≥5.0 x ULN	6/371 (1.6)	5/191 (2.6)	11/562 (2.0)
Blood Urea Nitrogen (mg/dL)			
Grade 1: 23 - 26	54/371 (14.6)	22/191 (11.5)	76/562 (13.5)
Grade 2: 27 - 31	42/371 (11.3)	25/191 (13.1)	67/562 (11.9)
Grade 3: >31	68/371 (18.3)	39/191 (20.4)	107/562 (19.0)
Creatinine (mg/dL)			
Grade 1: 1.1 - 1.3 x ULN	4/371 (1.1)	0/191 (0.0)	4/562 (0.7)
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	43/371 (11.6)	17/191 (8.9)	60/562 (10.7)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 - <2.0 x Baseline	102/371 (27.5)	55/191 (28.8)	157/562 (27.9)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x Baseline	75/371 (20.2)	31/191 (16.2)	106/562 (18.9)

Criterion†	Letermovir n/m (%)	Placebo n/m (%)	Total n/m (%)
HEMATOLOGY			
Hemoglobin (gm/dL)			
Grade 1: 10.0 - 10.9 (Male) / 9.5 - 10.4 (Female)	20/371 (5.4)	5/191 (2.6)	25/562 (4.4)
Grade 2: 9.0 - <10.0 (Male) / 8.5 - <9.5 (Female)	43/371 (11.6)	18/191 (9.4)	61/562 (10.9)
Grade 3: 7.0 - <9.0 (Male) / 6.5 - <8.5 (Female)	78/371 (21.0)	33/191 (17.3)	111/562 (19.8)
Grade 4: <7.0 (Male) / <6.5 (Female)	8/371 (2.2)	6/191 (3.1)	14/562 (2.5)
Platelet (10[3]/microL)			
Grade 1: 100 - <124.999	8/371 (2.2)	3/191 (1.6)	11/562 (2.0)
Grade 2: 50 - <100	12/371 (3.2)	11/191 (5.8)	23/562 (4.1)
Grade 3: 25 - <50	20/371 (5.4)	8/191 (4.2)	28/562 (5.0)
Grade 4: <25	50/371 (13.5)	19/191 (9.9)	69/562 (12.3)
Absolute Neutrophil Counts (10[3]/microL)			
Grade 1: 0.800 - 1.000	3/369 (0.8)	3/191 (1.6)	6/560 (1.1)
Grade 2: 0.600 - 0.799	5/369 (1.4)	6/191 (3.1)	11/560 (2.0)
Grade 3: 0.400 - 0.599	11/369 (3.0)	4/191 (2.1)	15/560 (2.7)
Grade 4: <0.400	27/369 (7.3)	14/191 (7.3)	41/560 (7.3)
Leukocytes (10[3]/microL)			
Grade 1: 2.0 - 2.499	10/371 (2.7)	11/191 (5.8)	21/562 (3.7)
Grade 2: 1.5 - 1.999	5/371 (1.3)	1/191 (0.5)	6/562 (1.1)
Grade 3: 1.0 - 1.499	8/371 (2.2)	4/191 (2.1)	12/562 (2.1)
Grade 4: <1.0	21/371 (5.7)	9/191 (4.7)	30/562 (5.3)

†For graded criteria: patients are counted once per test in the highest grade reported.

For baseline criteria: patients are counted in the '>X-fold Baseline' if the highest test value during treatment fell in this category. For baseline criteria: patients are counted in the '<X-fold Baseline' if the lowest test value during treatment fell in this category. n = Number of patients with post-baseline test results that met the predetermined criterion.

m = Number of patients with at least one post-baseline test result. For the criteria that involve a comparison to baseline, a baseline value is also required.

ULN = Upper limit of normal range.

Criteria based on Division of AIDS (DAIDS) 2014 Table for Grading the Severity of Adult and Pediatric Adverse Events

Supplementary Figures

Figure S1. Time to onset of clinically significant CMV infection, Safety Population.

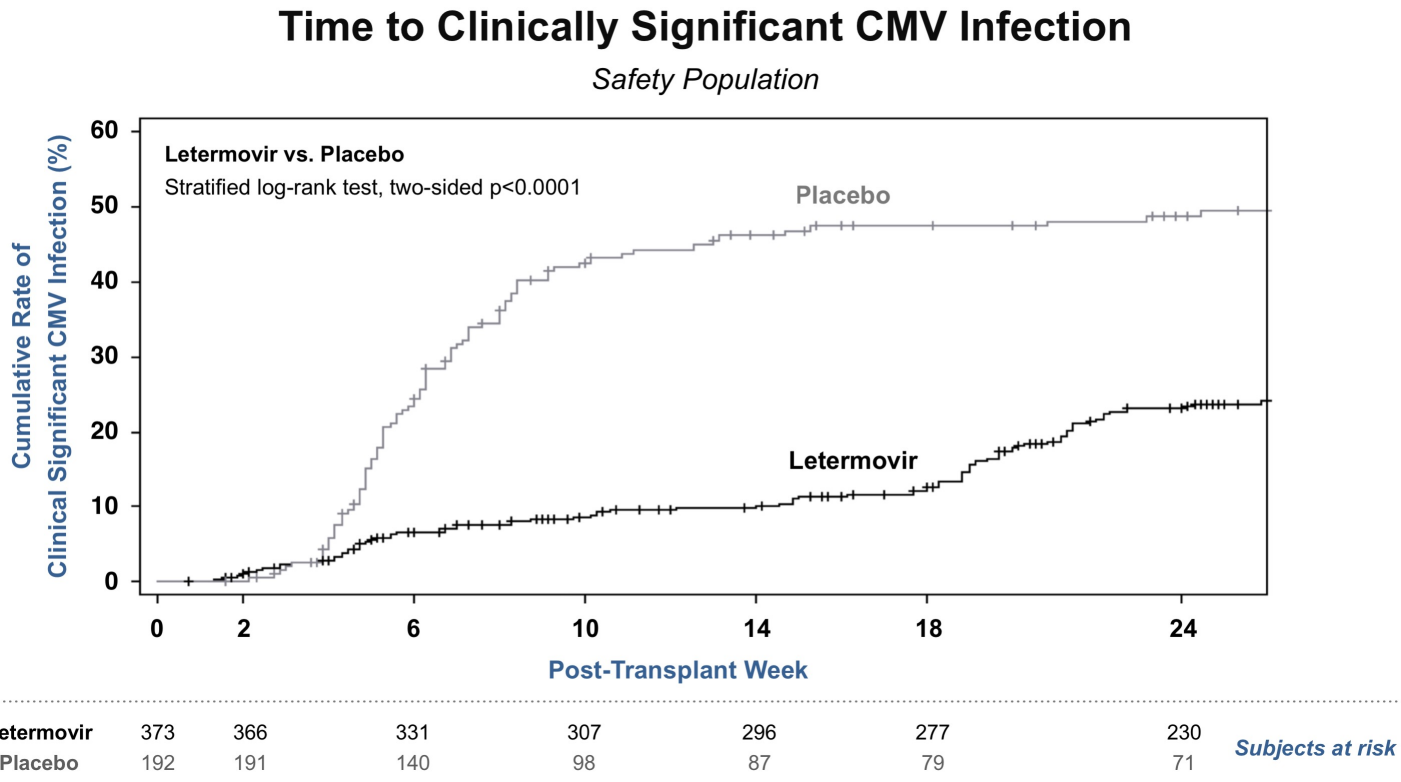


Figure S2. Time to onset of clinically significant CMV infection, patients with detectable CMV DNA at randomization (n=70).

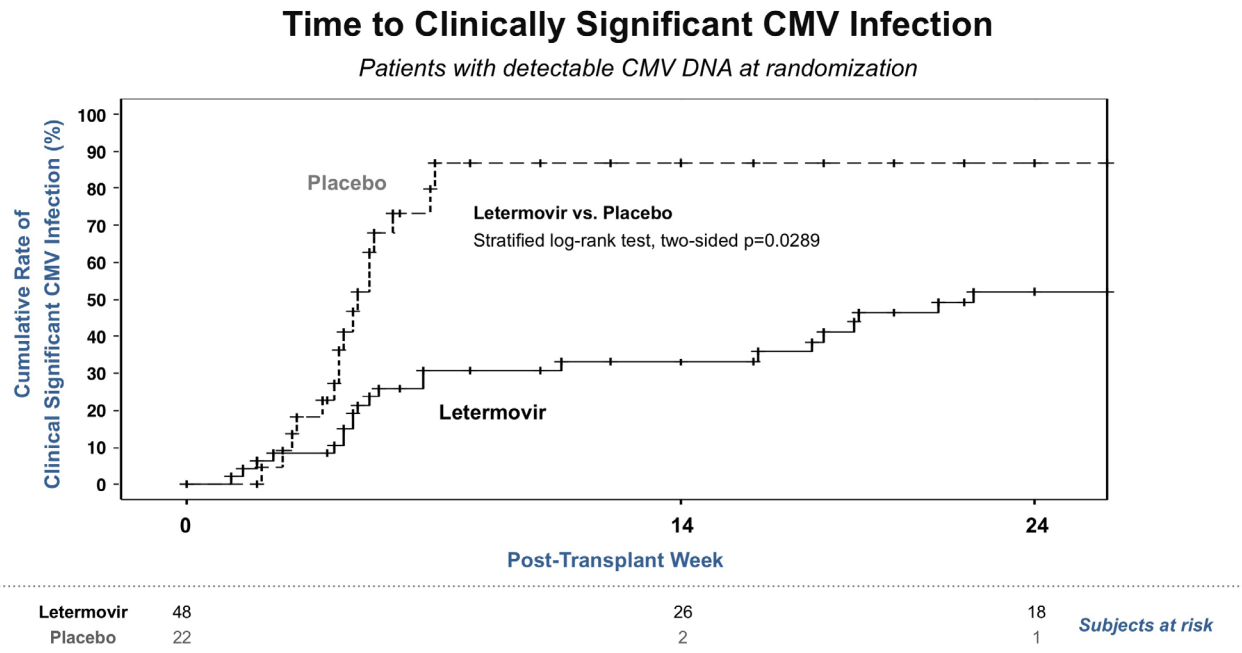


Figure S3. Non-Relapse Mortality by Treatment Group through Week 48 post-HCT, Primary Efficacy Population.

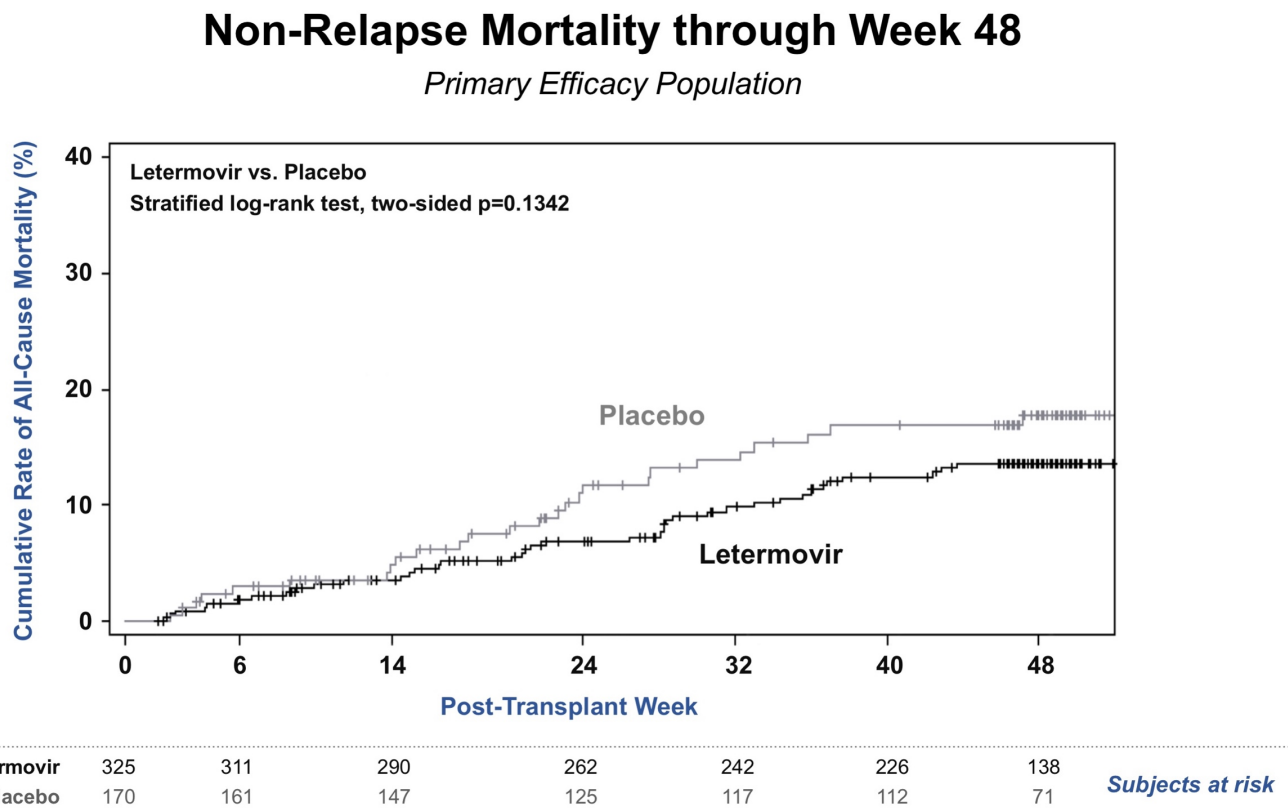
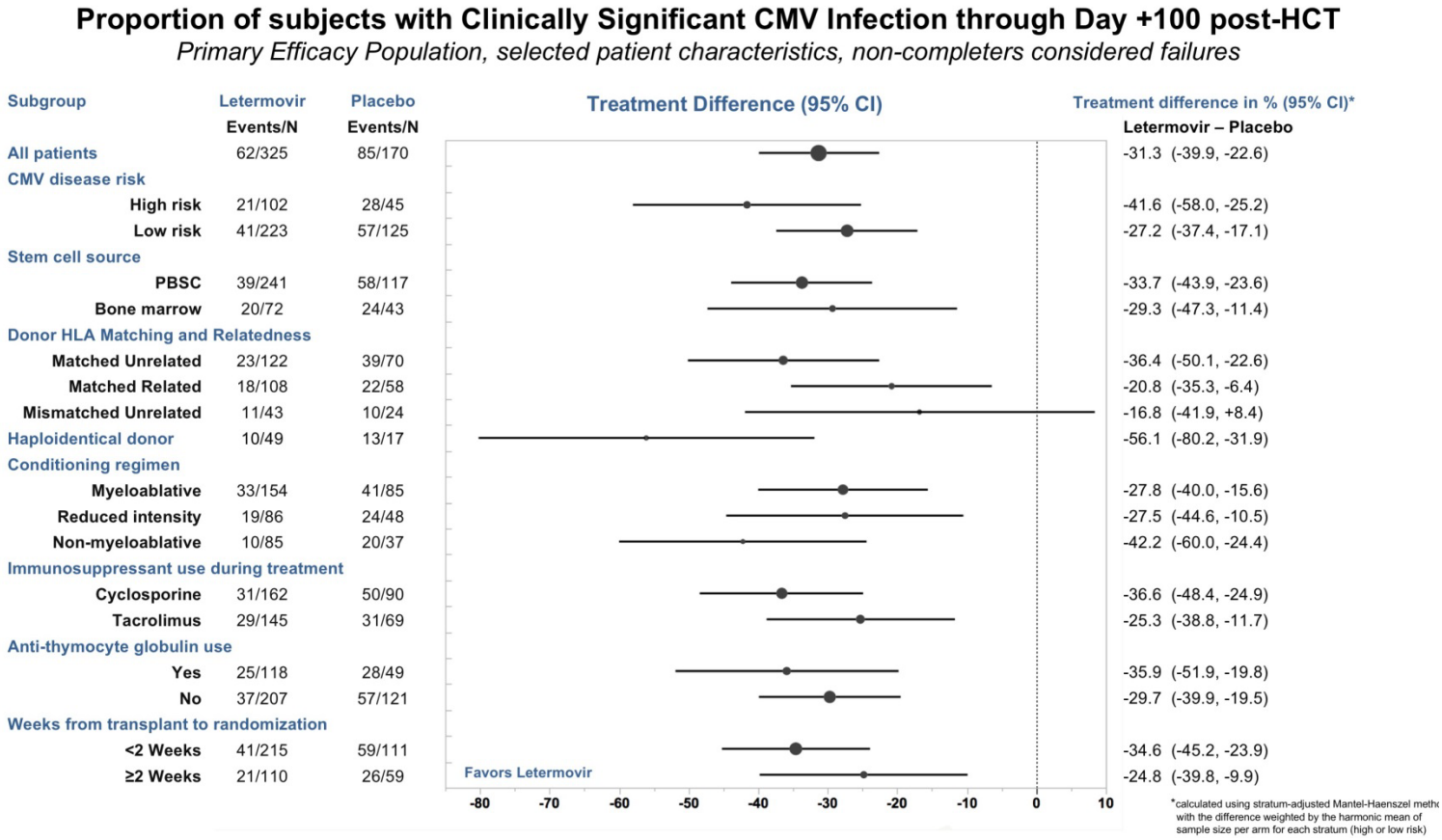
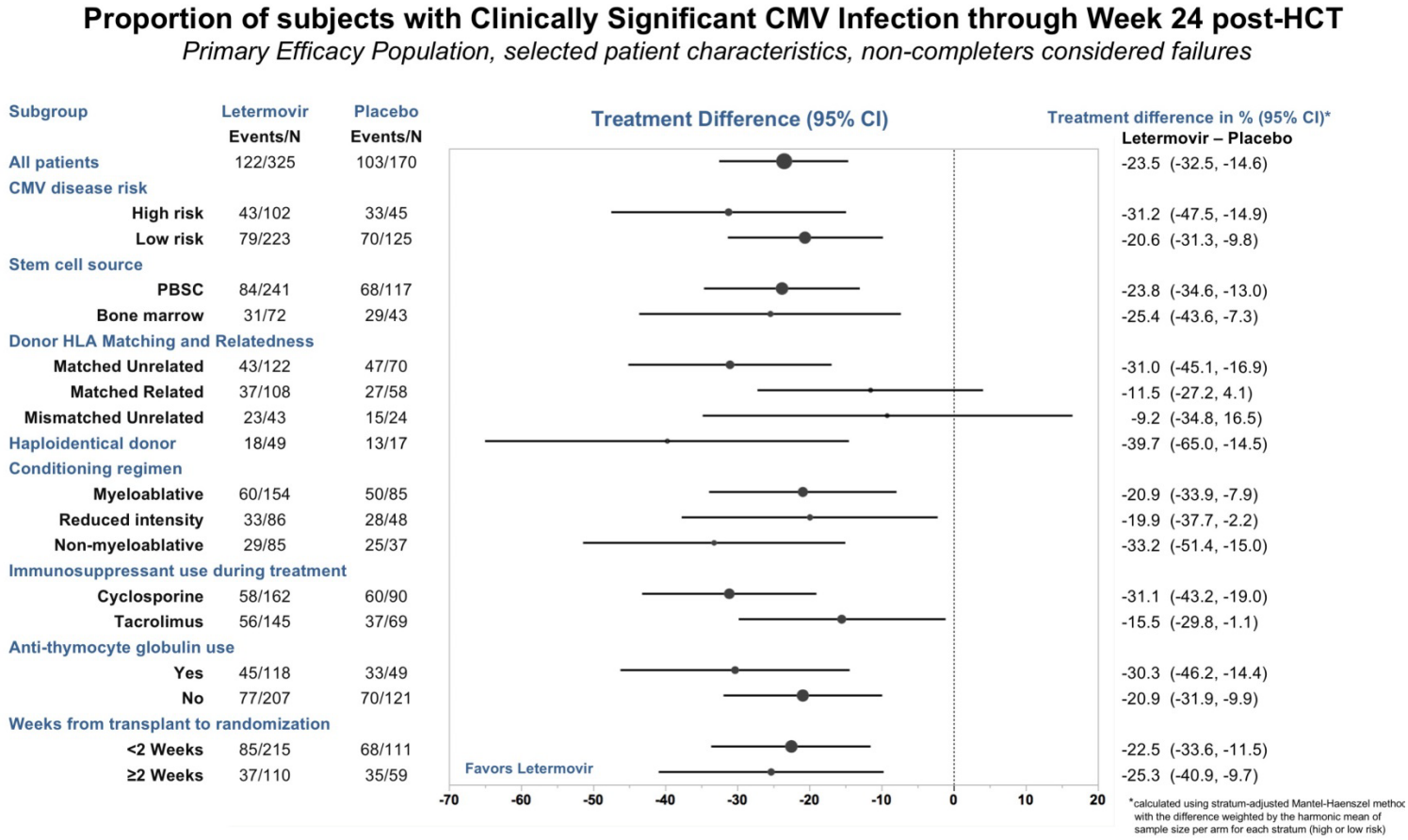


Figure S4. Forest plot of patients with clinically significant CMV infection through Day +100 post-HCT, selected patient characteristics, Primary Efficacy Population, using a non-completers considered failures approach.



Subgroup analyses were not conducted in categories that had less than 20 patients in the letermovir group or less than 10 patients in the placebo group, i.e. no estimate of treatment difference and confidence intervals were provided.

Figure S5. Forest plot of patients with clinically significant CMV infection through Week 24 post-HCT, selected patient characteristics, Primary Efficacy Population, using a non-completers considered failures approach.



Subgroup analyses were not conducted in categories that had less than 20 patients in the letermovir group or less than 10 patients in the placebo group, i.e. no estimate of treatment difference and confidence intervals were provided.

Figure S6. Time to neutrophil engraftment through Week 24 post-HCT among patients who started study drug before engraftment, Safety Population.

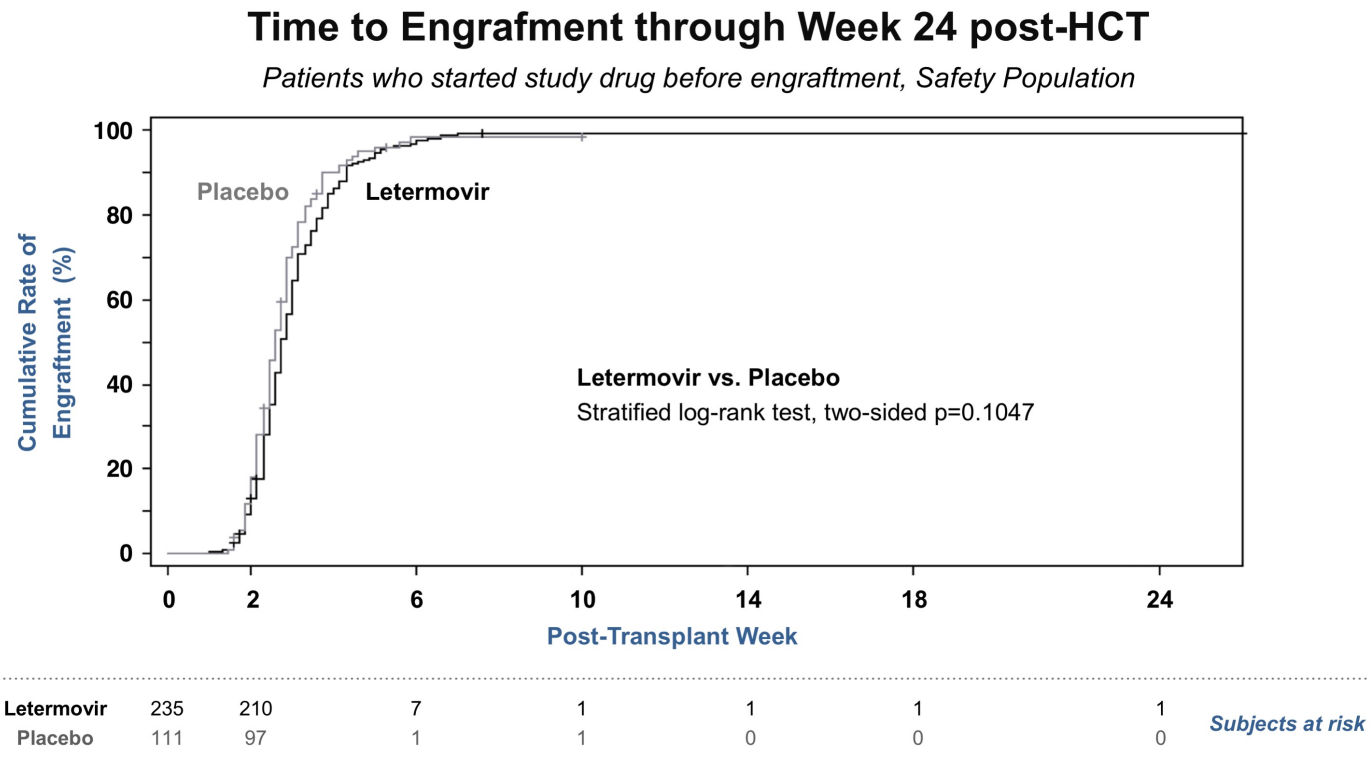
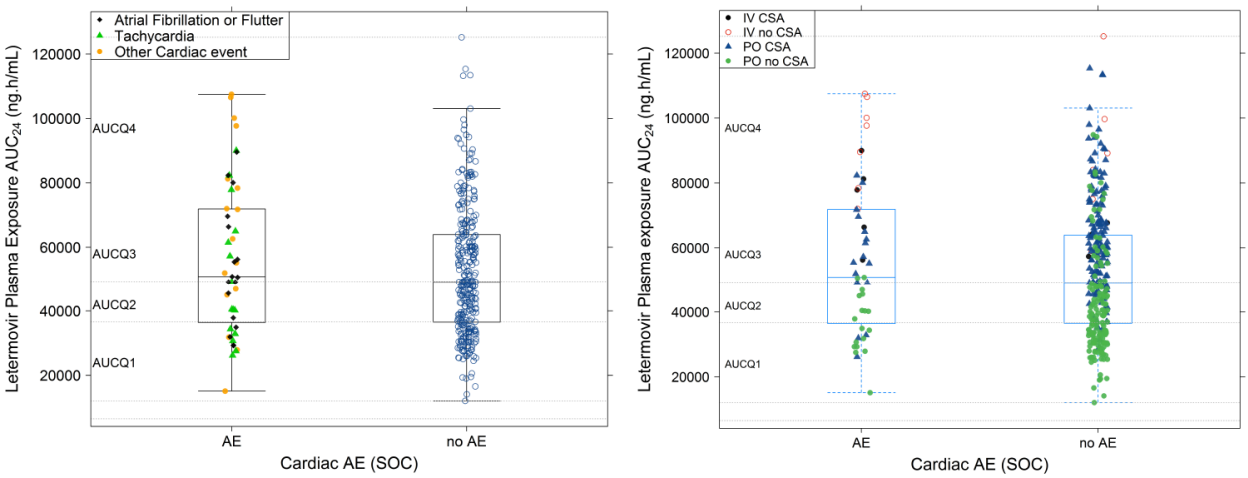
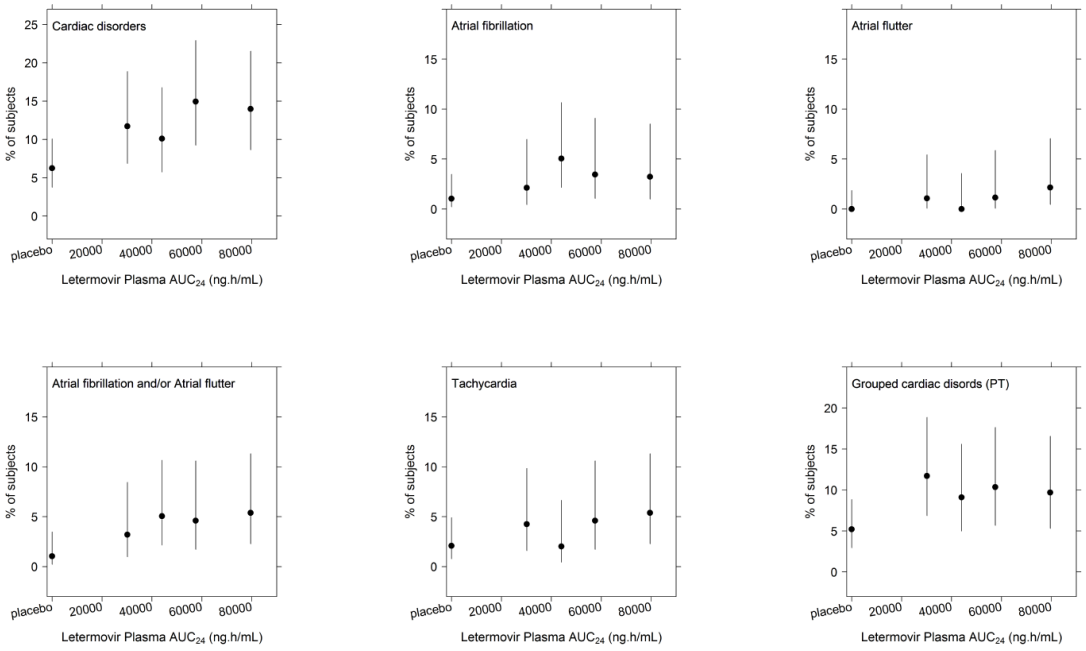


Figure S7. Letermovir plasma exposure in patients with and without cardiac adverse events by cardiac adverse event type and dosing regimen, Safety Population.



Some Jitter on x-axis was used to better visualize the individual exposures. **Dots:** Individual Exposure Estimates; **Boxes:** show the median, upper and lower quartiles (25% and 75%) of the data; **Whiskers:** Contain 100% of the data, except for statistical outliers (e.g: outside 1.5 times the interquartile range above the upper quartile and below the lower quartile).**Horizontal dashed lines:** boundaries of the 4 exposure (AUC_{24}) bins based on all subjects in the Letermovir treatment group.

Figure S8. Observed occurrence of cardiac disorders versus letermovir plasma exposure quartiles.



Data points and error bars depict the observed incidence rates and 90% CI in the placebo subjects (with assumed AUC_{24} of 0) and in the Letermovir subjects binned by exposure (AUC_{24}) quartiles versus the mean AUC_{24} of the bin.

Supplementary Appendix References

1. Little DJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in Clinincal Trials. N Eng J Med 2012;367(14):1355-60.
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3. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: Working definitions. Biol Blood Marrow Transplant 2009;15(12):1628–33.