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CADTH COMMON DRUG REVIEW

Clinical Review Report

LETERMOVIR (PREVYMIS)

(Merck Canada Inc.)

Indication: For the prophylaxis of cytomegalovirus (CMV) infection in adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
ASCT	allogeneic stem cell transplant
BMTS	Bone Marrow Transplant Subscale
CAP/CTM	Cobas AmpliPrep/Cobas TaqMan
CI	confidence interval
CMV	cytomegalovirus
ECOG-PSR	The Eastern Cooperative Oncology Group performance status rating
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	3-Level version of EuroQol 5-Dimensions
EQ VAS	EuroQol Visual Analogue Scale
FACT-BMT	Functional Assessment of Cancer Therapy — Bone Marrow Transplant
FACT-G	Functional Assessment of Cancer Therapy — General
FAS	full analysis set
GV	genotypic variant
GVHD	graft-versus-host disease
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
IFD	invasive fungal disease
IV	intravenous
KM	Kaplan–Meier
MCID	minimal clinically important difference
PCR	polymerase chain reaction
PET	pre-emptive therapy
PP	per-protocol

Drug	Letermovir (Prevymis)
Indication	For the prophylaxis of cytomegalovirus infection in adult cytomegalovirus -seropositive recipients of an allogeneic hematopoietic stem cell transplant
Reimbursement Request	As per indication
Dosage Form(s)	Intravenous infusion: 240 mg and 480 mg per vial Oral: 240 mg and 480 mg tablets
NOC Date	November 1, 2017
Manufacturer	Merck Canada Inc.

Executive Summary

Introduction

Important viruses to consider in hematopoietic stem cell transplant (HSCT) recipients include cytomegalovirus (CMV), which is a beta-herpesvirus that remains dormant in the human body after infection for life.[1-5] Although benign in patients with adequate immune function (patients remain asymptomatic CMV infection), patients with compromised immune systems such as those treated with radiation or chemotherapy before HSCT are at significantly increased risk of CMV infection, which can manifest into clinical complications.[1,6] Direct complications of active untreated CMV infection include the spectrum of CMV disease manifestations associated with morbidity and mortality, and can resemble infectious mononucleosis or include symptoms of pneumonia, hepatitis, encephalitis, seizures, or other illnesses. Indirect effects of CMV infection include increased risk of all-cause and non-relapse mortality, graft-versus-host disease (GVHD), and opportunistic bacterial/fungal infections.[2,5,7,8]

Generally, when considering patients at risk of CMV infection, pre-emptive therapy (PET) in combination with polymerase chain reaction (PCR) CMV DNA testing is preferred over prophylaxis to minimize antiviral toxicity. The most widely used antivirals for first-line PET are ganciclovir (for intravenous [IV] infusion) and valganciclovir (oral prodrug of ganciclovir). Generally, monitoring for CMV infection in a PET setting using PCR should be performed weekly in CMV-seropositive recipients of an HSCT until at least 100 days post-transplant.[9] Patients who are refractory to ganciclovir and valganciclovir can be treated with foscarnet; however, this antiviral is associated with considerable nephrotoxicity.[10] Cidofovir, another antiviral, is typically considered a third-line agent and is associated with both myelotoxicity and nephrotoxicity.[10] Both foscarnet and cidofovir are only available via the Health Canada Special Access Programme.

Letermovir is a novel inhibitor of CMV DNA terminase complex, belonging to a new antiviral class of quinazolines. It is administered either through IV infusion or orally (tablet) once daily to prevent CMV infection.[11,12] Letermovir is a CMV-specific antiviral with no effect on other herpesviruses and acts by inhibiting a component of the viral DNA terminase complex: subunit pUL56, involved in the DNA cleavage and packaging that has no equivalent target enzyme in the human body. Inhibiting subunit pUL56 cleaves newly

synthesized CMV DNA into individual viral genomes (affecting the formation of proper unit length) and guides them into empty viral capsids, disrupting the process required for viral DNA replication (i.e., disrupting virion maturation).[10,11,13]

According to the Health Canada–approved indication, letermovir can be used for the prophylaxis of CMV infection in adult CMV-seropositive recipients of an allogeneic HSCT.[11] Therefore, the objective of this review is to perform a systematic review of the beneficial and harmful effects of letermovir for the prophylaxis of CMV infection in adult CMV-seropositive recipients of an allogeneic HSCT.

Results and Interpretation

Included Studies

One trial met the inclusion criteria of the CADTH Common Drug Review (CDR) systematic review. Study P001 (N = 570) was a double-blind, placebo-controlled, multi-centre, multinational, phase III superiority randomized controlled trial and recruited patients from North America (including Canada). The study objective was to evaluate the efficacy and safety of letermovir as a preventive strategy for CMV infection in adults who are CMV-seropositive recipients of an allogeneic HSCT 24 weeks post-transplant. Patients were randomized to a 2:1 ratio of letermovir 480 mg per day administered orally or intravenously (240 mg per day when co-administered with cyclosporine) or matching placebo.

The primary efficacy end point was the incidence of clinically significant CMV infection through week 24 post-transplant, defined as an occurrence of either CMV end-organ disease or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the patient. Secondary outcomes included clinically significant CMV infection through week 14 post-transplant, initiation of PET, time to initiation of PET and CMV end-organ disease, as well as time to onset of CMV end-organ disease. Exploratory end points included mortality, opportunistic bacterial and/or fungal infections, GVHD, re-hospitalization, quality of life, and genotypic variance and resistance.

Limitations associated with the trial include no adjustments for multiple statistical testing other than the primary analysis of the primary efficacy end point, uncertainty regarding the durability of the treatment effect and patient outcomes beyond 48 weeks post-transplant, and the lack of comparative evidence versus a PET treatment strategy where PET is initiated at viral loads that are reflective of what would be seen in clinical practice (i.e., viral load ≥ 1,000 copies/mL, depending on patient risk factors).

Efficacy

Compared with placebo, letermovir was associated with a statistically significant reduction in clinically significant CMV infection at week 24 post-transplant (the primary outcome), using the primary method for imputing data (non-completers and missing data were considered to have met the primary end point). The stratum-adjusted mean difference was −23.5% (95% CI, −32.5 to −14.6) $P < 0.0001$ in favour of letermovir. The primary end point of clinically significant CMV infection was primarily driven by initiation of PET and the event rates for CMV end-organ disease were uncommon. The stratum-adjusted mean differences were −30.6% (95% CI, −40.2 to −21.0) $P < 0.0001$ and −0.4% (95% CI, −4.0 to 3.2) $P = 0.4056$, based on non-imputed methods (observed data only). Furthermore, results of the sensitivity analyses and subgroup analyses were mostly consistent with the primary analysis.

Secondary end points evaluated in Study P001 included clinically significant CMV infection through week 14 post-transplant (stratum-adjusted mean difference was −31.3% (95% CI, −39.9 to −22.6) $P < 0.0001$. The initiation of PET and CMV end-organ disease were also evaluated as secondary end points using imputed methods through week 14 and week 24 post-transplant. The stratum-adjusted mean differences were −31.0% (95% CI, −39.6 to −22.4) $P < 0.0001$ and −3.4% (95% CI, −10.0 to 3.3) $P = 0.1622$ through week 14 post-transplant and −23.3% (95% CI, −32.3 to -14.3) $P < 0.0001$ and −6.1% (95% CI, −14.4 to 2.2) $P = 0.0748$ through week 24 post-transplant, respectively. Overall, the results of the secondary outcomes were also consistent with the primary analysis in the reduction of clinically significant CMV infection; however, no adjustments for multiple statistical testing were made for any outcomes other than the primary analysis of the primary end point.

Time to onset of clinically significant CMV infection through week 24 post-transplant was also evaluated as a secondary outcome using Kaplan–Meier methods. An increase in the Kaplan–Meier rate of events can be observed between weeks 14 and 24 in the letermovir arm only. Therefore, the time to event end points evaluated in Study P001 may suggest a potential increase in clinically significant CMV infection when patients are no longer treated with letermovir, which implies uncertainty in the durability of the treatment effect.

Mortality was also evaluated as an exploratory end point in Study P001. Overall, the frequency of all-cause mortality, all-cause mortality in patients meeting the primary end point, and non-relapse related mortality was lower in the letermovir arm compared with the placebo arm through weeks 14, 24, and 48 post-transplant (all-cause mortality 5.2%, 9.8% and 18.8% compared with 7.1%, 15.9%, and 23.5%; CMV-related mortality was 0.3%, 0.9%, and 2.8% compared with 1.8%, 8.2%, and 13.5%; non-relapse related mortality was 4.0%, 6.5%, and 12.0% compared with 5.3%, 10.6%, and 15.9% in the letermovir and placebo arms, respectively).

Harms

Overall, a similar proportion of patients in the letermovir arm experienced (AEs) (97.9% and 100%, 98.1% and 100%, and 98.4% and 100%) and serious AEs (4.2% and 46.9%, 51.7% and 56.8%, and 54.2% and 59.9%) compared with the placebo arm through weeks 14, 24, and 48 post-transplant. A greater frequency of treatment withdrawal due to AEs was reported in the placebo arm compared with the letermovir arm (51.0% and 19.3%), which may be primarily due to a higher proportion of patients discontinuing due to CMV infection (6.2% and 39.1% in the letermovir and in the placebo arms, respectively).

The occurrence of notable harms — specifically, cardiac disorders and gastrointestinal disorders — was approximately equivalent in both treatment arms through weeks 14, 24, and 48 post-transplant, with the exception of cardiac disorders through week 14 post-transplant. Overall, more patients experienced cardiac disorders through week 14 post-transplant in the letermovir arm compared with the placebo arm (12.6% and 6.3%). The most common reasons for cardiac disorders were atrial fibrillation (3.5% and 1.0%), sinus tachycardia (1.1% and 1.6%), and tachycardia (4.0% and 2.1%). However, the differences between the two arms were lower through week 24 and 48 post-transplant (13.7% versus 9.9% and 14.2% versus 10.4% in the letermovir and placebo arms, respectively). The most common cardiac disorders through week 48 post-transplant in the letermovir and placebo arms were atrial fibrillation (3.5% and 1.0%), sinus tachycardia (1.1% and 2.6%), and tachycardia (4.8% and 2.6%), respectively.

A total of 74.8% and 73.4% experienced gastrointestinal disorders through week 48 post-transplant. The most common gastrointestinal disorders through week 48 post-transplant in the letermovir and placebo arms were abdominal pain (13.1% and 9.9%), diarrhea (29.5% and 28.6%), nausea (28.7% and 27.6%), and vomiting (21.4% and 18.2%), respectively.

In general, there were more deaths in the placebo arm through week 24 and 48 post-transplant compared with the letermovir arm (16.4% compared with 19.8%, and 21.7% compared with 24.5% in the letermovir and placebo arms, respectively). By contrast, there were more deaths in the letermovir arm through week 14 post-transplant compared with the placebo arm (10.2% and 8.9% in the letermovir and placebo arms respectively). The most frequently reported reasons for death through week 14 post-transplant (letermovir versus placebo) were GVHD (1.3% versus 1.6%), recurrent acute myeloid leukemia (1.9% versus 1.6%), septic shock (0.8% versus 1.6%), and sepsis (0.8% versus 0.5%). However, none of the deaths was considered to be related to study treatment by the investigators.

Prior to the availability of letermovir, prophylaxis with ganciclovir has been suggested as the most effective treatment for CMV disease; however, it may have limited use due to bone marrow toxicity.[14-16] High doses of other antivirals such as acyclovir and valacyclovir were reported to be less myelosuppressive than ganciclovir, although these agents also demonstrated inferior efficacy when compared with ganciclovir.[16-20] Given that both foscarnet and cidofovir can lead to severe myelotoxicity and nephrotoxicity, they are not the preferred agent for the management of CMV. Treatment with letermovir not only prevents clinically significant CMV infection compared with placebo, but should also result in fewer treatments with other more toxic antiviral agents such as ganciclovir.

Potential Place in Therapy[1]

CMV is one of the most common infections post-stem cell transplantation with both direct consequences (i.e., CMV disease) and indirect effects (e.g., increased risk of GVHD, invasive fungal infection, increased non-relapse mortality).[21] Some form of CMV preventive strategy is recommended for both seropositive recipients and seronegative recipients of seropositive donors in the first 100 days post-transplantation. This can either be in the form of primary prophylaxis or PET.

Currently, most centres use PET whereby patients are monitored via quantitative PCR or rarely antigenemia on a weekly basis. In general, most institutions in Canada choose to initiate PET in patients with CMV viremia > 1,000 copies/mL; however, some choose to initiate at lower thresholds for higher risk patients. Although IV ganciclovir is the only CMV-specific drug with proven efficacy in the prophylaxis setting, it comes with significant toxicity in the form of myelosuppression. Therefore, its preferred use is in a PET setting. Valganciclovir (oral prodrug formulation of ganciclovir) is also used for the management of CMV in a prophylactic setting; however, it has the same toxicity profile as the IV formulation of ganciclovir and no randomized trials to support its use as prophylaxis. Overall, PET strategies are reported to have reduced the incidence of CMV disease from a range of 20% to 30% to < 5% as reported in historical studies.[22] Despite the efficacy of currently available antivirals for the management of CMV, CMV reactivation can still occur and patients are at risk of the indirect effects noted earlier, especially those patients who are high risk for CMV reactivation.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Currently, PET has worked relatively well for reducing the incidence of CMV disease — particularly CMV pneumonia which had significant mortality.[21] It is not clear if PET has reduced the indirect effects of reactivation and prevention of CMV. However, according to the clinical experts consulted for this CDR submission, these benefits would be considered of importance to patients. Letermovir could potentially be used to prevent CMV and its consequences — including both the direct effects of end-organ disease and the indirect effects of reactivation — given that it was studied for prophylaxis and does not have the same myelosuppressive profile as other currently available antivirals. Still, letermovir's benefits on these indirect effects are not clear based on the results of Study P001.

According to the clinical experts consulted for this CDR submission, it is unlikely that letermovir would be used prophylactically in all allogenic HSCT recipients. This is in part because it is not clear from Study P001 if patients would still require monitoring for reactivation on a weekly basis as they do for PET. If monitoring is still required, then centres will likely not choose to use it broadly for all patients, given the cost and low incidence of CMV disease with the current strategy of PET. The use of prophylactic treatment would likely be started while a patient is in hospital, which is in contrast to the use of ganciclovir. Ganciclovir is most often given by home care (it is not part of the hospital budget) and, therefore, patients would transition to an insurer as soon as discharged. Alternatively, coverage could be included as part of transplant case costing (the per transplant amount of money a hospital gets per transplant) through Cancer Care Ontario. However, the clinical experts consulted indicated that this would not likely be on a pan-prophylactic basis.

A more likely scenario for the use of letermovir is in allogenic HSCT recipients who are at higher risk for viral reactivation. The definition of high risk would likely be similar to the criteria used in Study P001 (e.g., umbilical cord blood transplant recipients, haploidentical recipients, recipients of T-cell depleted grafts, recipients requiring high-dose steroids or other immunosuppression for acute GVHD) and patients receiving antithymocyte globulin or Campath (alemtuzumab). These patients have an unmet need, given the toxicity of the current prophylaxis, and were not excluded from the trial. In Canada, as most unrelated donor transplants use antithymocyte globulin, it is expected that about two-thirds of recipients would be considered high risk for CMV reactivation. According to the clinical experts consulted, the duration of coverage would be approximately 100 days post-stem cell transplant. Patients with prolonged or profound immunosuppression beyond 100 days (e.g., those with severe acute or chronic GVHD) and those who are at higher risk of CMV activation may need continuing prophylaxis and/or monitoring beyond 100 days post-transplant. These patients have an unmet need for either primary or secondary prophylaxis; although letermovir was not studied in this manner, it would likely be used for these arms.

Secondary prophylaxis for patients with CMV disease pre-transplant who are considered at risk for a recurrence are another risk arm who would benefit from prophylaxis. This may be of particular interest to patients for whom the virus was slow to clear the first time or there were significant issues with ganciclovir therapy (toxicity or not conveniently available for distant patients).These patients have an unmet need but were excluded from this trial. Given that letermovir is suggested to have no cross-resistance to other antivirals, and has no issues with myelosuppression, there could be interest in using letermovir as primary therapy instead of ganciclovir for resistant strains of CMV.

Finally, the largest unmet need currently is for patients requiring therapy who are refractory or resistant to ganciclovir or valganciclovir. These patients often require more toxic drugs

(i.e., foscarnet, cidofovir) with varying efficacy. Letermovir was not studied for treatment in these patients; however, letermovir would likely be used for these patients if it were widely available.

Conclusions

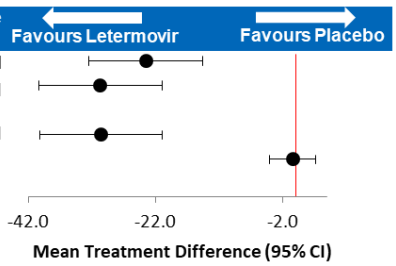
The CDR systematic review included one double-blind, phase III, placebo-controlled randomized controlled trial (Study P001). It was designed to assess the benefits and harms of letermovir compared with placebo as a preventive strategy for clinically significant CMV infection in adults who are CMV-seropositive recipients of an allogeneic HSCT defined as occurring from either CMV end-organ disease or the initiation of PET, based on documented CMV viremia and the clinical condition of the patient.

Letermovir was associated with a statistically significant reduction when compared with placebo for the prevention of clinically significant CMV infection through week 24 post-transplant (primary end point). This was mainly driven by the initiation of PET. The results of secondary end points (clinically significant CMV infection through week 14 post-transplant, and initiation of PET at 14 and 24 weeks post-transplant) were supportive of the primary analysis. However, no adjustments for multiple statistical testing were made. There were no statistically significant differences between letermovir and placebo for the occurrence of CMV end-organ disease at 14 and 24 weeks post-transplant.

A similar percentage of patients in the letermovir arm experienced AEs and serious AEs compared with the placebo arm through weeks 14, 24, and 48 post-transplant. The occurrence of notable harms — specifically, gastrointestinal disorders — was approximately similar in both treatment arms through weeks 14, 24, and 48 post-transplant. Cardiac disorders were more common in patients receiving letermovir compared with placebo through week 14 post-transplant; however, the differences between the two arms diminished through week 24 and 48 post-transplant.

Table 1: Clinically Significant Cytomegalovirus Infection Through Week 24 Post-Transplant (Full Analysis Set)

End Point	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value
Clinically Significant CMV infection[ab]	**122/325 (37.5)**	**103/170 (60.6)**	**−23.5 (-32.5, -14.6)**	**< 0.0001**
Clinically significant CMV infection by week 24[c]	57/260 (21.9)	71/138 (51.4)	−30.7 (-40.3, -21.0)	< 0.0001
Initiation of PET based on documented CMV viremia[c]	52/258 (20.2)	68/137 (49.6)	−30.6 (-40.2, -21.0)	< 0.0001
CMV end-organ disease[c]	5/254 (2.0)	3/123 (2.4)	−0.4 (-4.0, 3.2)	0.4056
Discontinued from study before week 24	56/325 (17.2)	27/170 (15.9)		
Missing outcome in week 24 visit window	9/325 (2.8)	5/170 (2.9)		



CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; *P* = probability; PET = pre-emptive therapy.

Note: Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the patient. Ninety-five per cent CIs and *P* value for the treatment differences in per cent response were calculated using a stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided *P* value ≤ 0.0249 was used for declaring statistical significance. No adjustments for multiple statistical tests were made for any outcomes other than the primary efficacy end point.

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

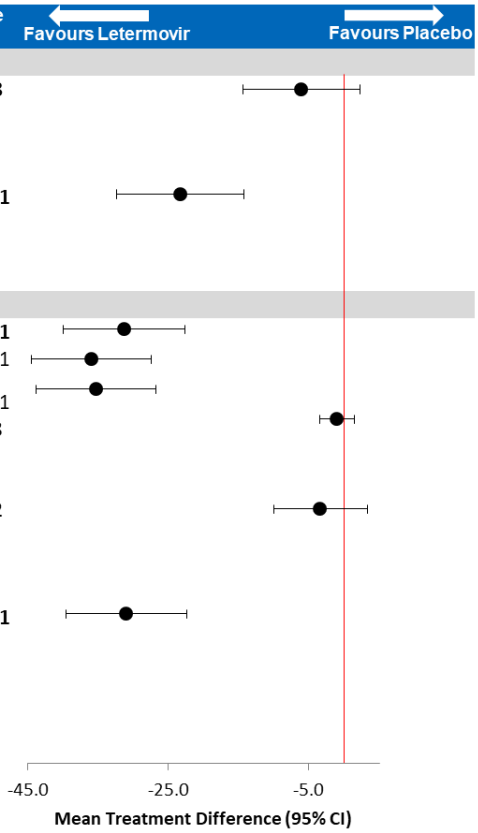
[b] The primary analysis included all patients who developed clinically significant CMV infection or prematurely discontinued being in the study or had a missing outcome through week 24 post-transplant visit window.

[c] Sensitivity analysis of the primary end point based on observed data only; missing data for a particular end point was excluded from the analysis.

Source: P001 V01 CSR.[23]

Table 2: Initiation of Pre-Emptive Therapy and Cytomegalovirus End-Organ Disease Through Week 24/14 Post-Transplant (Full Analysis Set)

End Point	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value
Week 24 Post-Transplant				
CMV End-Organ Disease[ab]	**76/325 (23.4)**	**50/170 (29.4)**	**−6.1 (-14.4, 2.2)**	**0.0748**
CMV end-organ disease	5/325 (1.5)	3/170 (1.8)		
Discontinued from study before week 24	61/325 (18.8)	38/170 (22.4)		
Missing outcome in week 24 visit window	10/325 (3.1)	9/170 (5.3)		
Initiation of PET[ab]	**119/325 (36.6)**	**101/170 (59.4)**	**−23.3 (-32.3, -14.3)**	**< 0.0001**
Initiation of PET for documented CMV viremia	52/325 (16)	68/170 (40)		
Discontinued from study before week 24	57/325 (17.5)	28/170 (16.5)		
Missing outcome in week 24 visit window	10/325 (3.1)	5/170 (2.9)		
Week 14 Post-Transplant				
Clinically Significant CMV Infection[ab]	**62/325 (19.1)**	**85/170 (50)**	**−31.3 (-39.9, -22.6)**	**< 0.0001**
Clinically significant CMV infection by week 14[c]	25/288 (8.7)	67/152 (44.1)	−36.0 (-44.5, -27.4)	< 0.0001
Initiation of PET based on documented CMV viremia[c]	24/288 (8.3)	65/151 (43.0)	−35.3 (-43.8, -26.8)	< 0.0001
CMV end-organ disease[c]	1/285 (0.4)	2/170 (1.4)	−1.0 (-3.5, 1.5)	0.2258
Discontinued from study before week 14	33/325 (10.2)	16/170 (9.4)		
Missing outcome in week 14 visit window	4/325 (1.2)	2/170 (1.2)		
CMV End-Organ Disease[ab]	**41/325 (12.6)**	**27/170 (15.9)**	**−3.4 (-10.0, 3.3)**	**0.1622**
CMV end-organ disease	1/325 (0.3)	2/170 (1.2)		
Discontinued from study before week 14	35/325 (10.8)	20/170 (11.8)		
Missing outcome in week 14 visit window	5/325 (1.5)	5/170 (2.9)		
Initiation of PET[ab]	**61/325 (18.8)**	**84/170 (49.4)**	**−31.0 (-39.6, -22.4)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	24/325 (7.4)	65/170 (38.2)		
Discontinued from study before week 14	33/325 (10.2)	17/170 (10)		
Missing outcome in week 14 visit window	4/325 (1.2)	2/170 (1.2)		



CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; *P* = probability; PET = pre-emptive therapy.

Note: Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the patient. Ninety-five per cent CIs and *P* value for the treatment differences in per cent response were calculated using stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided *P* value ≤ 0.0249 was used for declaring statistical significance. No adjustments for multiple statistical tests were made for any outcomes other than the primary efficacy end point.

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[b] The primary analysis included all patients who developed clinically significant CMV infection or prematurely discontinued being in the study or had a missing outcome through week 24 post-transplant visit window.

[c] Sensitivity analysis of the secondary end point based on observed data only; missing data for a particular end point was excluded from the analysis.

Source: P001 V01 CSR.[23]

Table 3: Summary of Harms (All Patients as Treated)

Harms, n (%)	Week 14		Week 24		Week 48	
	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192
AEs						
Patients with > 0 AEs	365 (97.9)	192 (100)	366 (98.1)	192 (100)	367 (98.4)	192 (100)
Most Common AEs[a]						
Febrile neutropenia	31 (8.3)	18 (9.4)	33 (8.8)	21 (10.9)	35 (9.4)	21 (10.9)
Fatigue	50 (13.4)	21 (10.9)	52 (13.9)	25 (13.0)	55 (14.7)	26 (13.5)
Mucosal inflammation	46 (12.3)	24 (12.5)	47 (12.6)	24 (12.5)	47 (12.6)	24 (12.5)
Edema peripheral	54 (14.5)	18 (9.4)	57 (15.3)	22 (11.5)	60 (16.1)	23 (12.0)
Pyrexia	77 (20.6)	43 (22.4)	86 (23.1)	50 (26.0)	92 (24.7)	53 (27.6)
Blood creatinine increased	36 (9.7)	13 (6.8)	38 (10.2)	15 (7.8)	40 (10.7)	15 (7.8)
Decreased appetite	38 (10.2)	22 (11.5)	40 (10.7)	25 (13.0)	44 (11.8)	28 (14.6)
Back pain	23 (6.2)	14 (7.3)	24 (6.4)	20 (10.4)	24 (6.4)	20 (10.4)
Headache	52 (13.9)	18 (9.4)	57 (15.3)	23 (12.0)	60 (16.1)	24 (12.5)
Acute kidney injury	36 (9.7)	25 (13.0)	41 (11.0)	29 (15.1)	41 (11.0)	29 (15.1)
Cough	53 (14.2)	20 (10.4)	62 (16.6)	28 (14.6)	62 (16.6)	27 (14.1)
Rash	76 (20.4)	41 (21.4)	86 (23.1)	48 (25.0)	90 (24.1)	51 (26.6)
Hypertension	31 (8.3)	21 (10.9)	32 (8.6)	23 (12.0)	34 (9.1)	24 (12.5)
SAEs						
Patients with > 0 SAEs	165 (44.2)	90 (46.9)	193 (51.7)	109 (56.8)	202 (54.2)	115 (59.9)
Most Common SAEs[b]						
Diarrhea	2 (0.5)	5 (2.6)	3 (0.8)	5 (2.6)	3 (0.8)	5 (2.6)
Multiple organ dysfunction syndrome	0	2 (1.0)	1 (0.3)	4 (2.1)	2 (0.5)	4 (2.1)
Pyrexia	7 (1.9)	4 (2.1)	9 (2.4)	4 (2.1)	10 (2.7)	4 (2.1)
Pneumonia	8 (2.1)	3 (1.6)	14 (3.8)	4 (2.1)	15 (4.0)	6 (3.1)
Sepsis	5 (1.3)	2 (1.0)	7 (1.9)	3 (1.6)	8 (2.1)	4 (2.1)
Septic shock	4 (1.1)	5 (2.6)	5 (1.3)	6 (3.1)	5 (1.3)	7 (3.6)
Acute myeloid leukemia	4 (1.1)	2 (1.0)	5 (1.3)	4 (2.1)	7 (1.9)	4 (2.1)
Acute myeloid leukemia recurrent	11 (2.9)	7 (3.6)	20 (5.4)	14 (7.3)	23 (6.2)	17 (8.9)
Acute kidney injury	5 (1.3)	9 (4.7)	7 (1.9)	9 (4.7)	7 (1.9)	9 (4.7)
WDAEs						
WDAEs	NR	NR	6 (1.6)	3 (1.5)	NR	NR
Treatment WDAEs						
Patients with > 0 WDAEs	72 (19.3)	98 (51.0)	72 (19.3)	98 (51.0)	73 (19.6)	99 (51.6)
Most Common Reasons[c]						
Nausea	6 (1.6)	2 (1.0)	NA	NA	NA	NA
Venoocclusive liver disease	2 (0.5)	2 (1.0)	NA	NA	NA	NA
Graft versus host disease	3 (0.8)	2 (1.0)	NA	NA	NA	NA
Cytomegalovirus infection	23 (6.2)	75 (39.1)	NA	NA	NA	NA
Septic shock	1 (0.3)	2 (1.0)	NA	NA	NA	NA
Acute myeloid leukemia recurrent	4 (1.1)	1 (0.5)	NA	NA	NA	NA
Deaths						
Number of deaths	38 (10.2)	17 (8.9)	61 (16.4)	38 (19.8)	81 (21.7)	47 (24.5)

Harms, n (%)	Week 14		Week 24		Week 48	
	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192
Notable Harms[b]						
Cardiac Disorders	**47 (12.6)**	**12 (6.3)**	**51 (13.7)**	**19 (9.9)**	**53 (14.2)**	**20 (10.4)**
Atrial fibrillation	13 (3.5)	2 (1.0)	13 (3.5)	2 (1.0)	13 (3.5)	2 (1.0)
Sinus tachycardia	4 (1.1)	3 (1.6)	4 (1.1)	5 (2.6)	4 (1.1)	5 (2.6)
Tachycardia	15 (4.0)	4 (2.1)	16 (4.3)	5 (2.6)	18 (4.8)	5 (2.6)
Gastrointestinal Disorders	**261 (70.0)**	**129 (67.2)**	**272 (72.9)**	**137 (71.4)**	**279 (74.8)**	**141 (73.4)**
Abdominal distension	4 (1.1)	3 (1.6)	4 (1.1)	4 (2.1)	4 (1.1)	5 (2.6)
Abdominal pain	44 (11.8)	18 (9.4)	48 (12.9)	19 (9.9)	49 (13.1)	19 (9.9)
Abdominal pain upper	15 (4.0)	16 (8.3)	19 (5.1)	16 (8.3)	23 (6.2)	17 (8.9)
Constipation	27 (7.2)	20 (10.4)	30 (8.0)	22 (11.5)	31 (8.3)	22 (11.5)
Diarrhea	97 (26.0)	47 (24.5)	105 (28.2)	52 (27.1)	110 (29.5)	55 (28.6)
Dry mouth	20 (5.4)	6 (3.1)	21 (5.6)	11 (5.7)	21 (5.6)	11 (5.7)
Flatulence	4 (1.1)	4 (2.1)	5 (1.3)	4 (2.1)	5 (1.3)	4 (2.1)
Dyspepsia	20 (5.4)	7 (3.6)	5 (1.3)	10 (5.2)	21 (5.6)	7 (3.6)
Gastroesophageal reflux disease	4 (1.1)	9 (4.7)	20 (5.4)	7 (3.6)	6 (1.6)	11 (5.7)
Haematochezia	4 (1.1)	2 (1.0)	5 (1.3)	10 (5.2)	4 (1.1)	4 (2.1)
Hemorrhoids	18 (4.8)	4 (2.1)	19 (5.1)	5 (2.6)	18 (4.8)	6 (3.1)
Lip dry	3 (0.8)	3 (1.6)	4 (1.1)	4 (2.1)	5 (1.3)	5 (2.6)
Nausea	9 (26.5)	45 (23.4)	102 (27.3)	50 (26.0)	107 (28.7)	53 (27.6)
Esophagitis	3 (0.8)	3 (1.6)	4 (1.1)	3 (1.6)	4 (1.1)	4 (2.1)
Stomatitis	23 (6.2)	9 (4.7)	23 (6.2)	13 (6.8)	24 (6.4)	14 (7.3)
Vomiting	69 (18.5)	26 (13.5)	74 (19.8)	32 (16.7)	80 (21.4)	35 (18.2)

AE = adverse event; CSR = Clinical Study Report; N = total number in the sample under study; n = number in a subgroup of the sample under study; NA = not applicable; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency ≥ 10%.

[b] Frequency ≥ 2%.

[c] Frequency ≥ 1%.

Source: P001 V01 CSR[23], P001 V02 CSR.[24]

Introduction

Disease Prevalence and Incidence

Hematopoietic stem cell transplantation (HSCT), using patients' (autologous) or donor-provided (allogeneic) hematopoietic stem cells, involves the intravenous (IV) infusion of stem cells to re-establish hematopoietic function. HSCT can potentially be a curative therapy for malignancies, severe aplastic anemia, and rare inborn errors of metabolism or primary immunodeficiencies.[25-30] Despite good donor/recipient matching, HSCT typically still requires immunosuppressive medications to mitigate graft-versus-host disease (GVHD).[25,26,31] The immunosuppression associated with HSCT also commonly allows micro-organisms to cause infection more easily, even those with limited pathogenicity.[26,31]

Important viruses to consider in HSCT recipients include cytomegalovirus (CMV), which is a beta-herpesvirus that remains dormant in the human body after primary infection for life.[1-5] Although benign in patients with adequate immune function (patients remain asymptomatic despite CMV infection), patients with compromised immune systems such as those treated with radiation or chemotherapy before HSCT are at significantly increased risk of CMV infection, which can manifest into clinical complications.[1,6] Direct complications of active untreated CMV infection include the spectrum of CMV disease manifestations associated with morbidity and mortality, and can resemble infectious mononucleosis or include symptoms of pneumonia, hepatitis, encephalitis, seizures, or other illnesses. Indirect effects of CMV infection include increased risk of all-cause and non-relapse mortality, GVHD, and opportunistic bacterial/fungal infections.[2,5,7,8]

Generally, CMV infection can occur after HSCT for a variety of reasons, including CMV seropositivity of the transplant (i.e., a seropositive donor) or infection of dormant CMV infection (i.e., a seropositive recipient).[32] The risk for CMV infection also depends on the HSCT recipient and donor CMV-serostatus among other factors, such as immunosuppression. However, the most important risk factor post-allogeneic HSCT is CMV seropositivity of the transplant recipient.[33-36] In fact, due to the impaired cellular immunity as a result of the induction and conditioning regimen, infection of the latent virus is the dominant mechanism of infection in immunocompromised patients.[33] Furthermore, patients with a history of CMV disease (e.g., pneumonitis, gastrointestinal disease, and retinitis) six months prior to HSCT are at a very high risk for infection (and death).[35,37] Therefore, donors for allogeneic HSCT should be selected based on serostatus to mitigate risk of CMV infection.

The Canadian Institute for Health Information reported that the number of autologous and allogeneic HSCT procedures in Canada has increased steadily, from 1,236 in 2010 to 1,605 in 2014, and that approximately 47% of those transplants were allogeneic HSCTs.[38,39] The Center for International Blood and Marrow Transplant Research reported that among the 9,469 allogeneic HSCTs performed between 2003 and 2010 (including at sites in Canada), approximately 62% were performed in CMV-seropositive recipients (those considered at high risk for CMV infection).[5] Similarly, other studies conducted in Canada and the US have shown a similar prevalence of seropositive recipients undergoing HSCT (approximately 50%).[33,36,38,40-42]

Standards of Therapy

Current therapies for the management of CMV infection can be categorized into three groups:

- primary prophylaxis (which involves the administration of antiviral drugs to prevent primary infection in patients at increased risk)
- secondary prophylaxis (which involves the administration of prophylactic dosages of antiviral drugs to prevent CMV infection following primary infection)
- pre-emptive therapy (PET) (which involves initiation of antiviral therapy based on serial screening with a sensitive polymerase chain reaction [PCR] assay in an attempt to detect early infection, mitigating the occurrence of CMV disease).[10]

Prophylaxis for the management of CMV post-HSCT has been studied using antiviral drugs (DNA polymerase inhibitors), including acyclovir, valacyclovir, valganciclovir, ganciclovir, foscarnet, and cidofovir.[13-20,43-45] Prior to the availability of letermovir, prophylaxis with ganciclovir has been suggested as the most effective treatment for CMV disease; however, it may have limited use due to bone marrow toxicity.[14-16] High doses of acyclovir and valacyclovir were reported to be less myelosuppressive than ganciclovir, although these agents also demonstrated inferior efficacy when compared with ganciclovir.[16-20] Given that both foscarnet and cidofovir can lead to severe renal impairment, they are not typically used in a prophylactic setting. Therefore, although not used in clinical practice, current CMV prophylaxis is thought to be best reserved for patients at the highest risk of CMV infection (i.e., recipients of a transplant from seropositive donors who received T-cell depleted allografts, human leukocyte antigen-mismatched allograft or an umbilical cord blood graft).[10]

The most widely used antivirals for first-line PET (Table 4) are ganciclovir (for IV infusion) and valganciclovir (oral prodrug of ganciclovir). Generally, monitoring for CMV infection in a PET setting using PCR should be performed weekly in CMV-seropositive recipients of an HSCT until at least 100 days post-transplant.[9] In patients at higher risk of CMV infection (e.g., recipients of a transplant from seropositive donors who received T-cell depleted allografts, human leukocyte antigen-mismatched allograft, an umbilical cord blood graft or those who are significantly immunosuppressed), PCR monitoring in a PET setting can be performed twice weekly to ensure timely treatment.[10] Patients who are refractory to ganciclovir and valganciclovir can be treated with foscarnet; however; this antiviral is associated with considerable nephrotoxicity.[10] Cidofovir, another antiviral, is typically considered a third-line agent and is associated with both myelotoxicity and nephrotoxicity.[10] Both foscarnet and cidofovir are only available through Health Canada's Special Access Programme.

Given that all currently available antivirals are DNA polymerase inhibitors, cross-resistance to ganciclovir and valganciclovir can occur from mutations in the UL97 subunit protein, while mutations in UL54 can confer multi-drug resistance, including to foscarnet and cidofovir.[46,47] Overall, it has been reported that 2% to 8% of patients treated for CMV develop some type of drug resistance.[48]

Drug

Letermovir is a novel inhibitor of CMV DNA terminase complex belonging to a new antiviral class of quinazolines and is administered once daily either through an IV infusion or orally (tablet) to prevent CMV infection.[12] Letermovir is a CMV-specific antiviral with no effect on

other herpesviruses and acts by inhibiting a component of the viral DNA terminase complex (subunit pUL56, involved in the DNA cleavage and packaging that has no equivalent target enzyme in the human body). Inhibiting subunit pUL56 cleaves newly synthesized CMV DNA into individual viral genomes (affecting the formation of proper unit length) and guides them into empty viral capsids, disrupting the process required for viral DNA replication (i.e., disrupting virion maturation).[10,11,13]

Given letermovir's distinct mechanism of action, no cross-resistance has been demonstrated between letermovir and currently available antivirals used in the management of CMV.[12] Some studies have also reported that letermovir may be active against certain strains of CMV that are resistant to currently available antivirals.[12,49] Furthermore, prophylaxis with letermovir appears to avoid the myelosuppressive effects and other toxicities associated with ganciclovir prophylaxis.[10]

According to the Health Canada–approved indication, letermovir can be used for the prophylaxis of CMV infection in adult CMV-seropositive recipients of an allogeneic HSCT.[11] The Health Canada–approved dosage of letermovir is 480 mg administered once daily (for both the IV and oral formulation). If co-administered with cyclosporine, the dosage of letermovir should be decreased to 240 mg once daily. The recommended treatment regimen as per the Health Canada–approved product monograph indicates that letermovir should be initiated post-HSCT and may be started on the day of transplant or up to no later than 28 days post-transplant, and should continue through 100 days post-HSCT. Overall, the Health Canada–approved product monograph reports that treatment with letermovir may be associated with increased gastrointestinal disorders and cardiac disorders. There are currently no other approved prophylactic agents for the management of CMV in Canada.

Letermovir is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. Letermovir is also contraindicated in patients concomitantly treated with pimozide and ergot alkaloids due to QT prolongation and torsades de pointes and ergotism, respectively.[11]

Table 4: Key Characteristics of Ganciclovir and Valganciclovir

	Letermovir	Ganciclovir	Valganciclovir
Mechanism of Action	Inhibiting a component of the viral DNA terminase complex (subunit pUL56, involved in the DNA cleavage and packaging)	Competitively inhibiting dGTP incorporation into DNA by DNA polymerase and by incorporating into viral DNA subsequently causing termination or very limited viral DNA elongation.	
Indication[a]	For the prophylaxis of CMV infection in adult CMV-seropositive recipients of an allogeneic HSCT	For the prevention of CMV disease in transplant recipients at risk for CMV disease	For the prevention of CMV disease in solid organ transplant patients who are at risk
Route of Administration	Oral	IV	Oral
Recommended Dosage	480 mg administered once daily (for both the IV and oral formulation). If co-administered with cyclosporine, the dosage of letermovir should be decreased to 240 mg once daily. Letermovir should be started after HSCT (before or after engraftment); it may be started on the day of transplant, no later than 28 days post-transplant, and continued through 100 days post-transplant.	**Initial Dosage:** 5 mg/kg every 12 hours for 7 to 14 days, followed by either 5 mg/kg once per day if on a 7-day weekly regimen, or 6 mg/kg once per day if on a 5-day weekly regimen, given as a constant intravenous infusion over one hour. The duration of treatment depends on the duration and degree of immunosuppression. Typically 100 days to 120 days post-transplant.	900 mg once daily (with food) starting within 10 days of transplantation and continuing until 100 days post-transplant.
Serious Side Effects / Safety Issues	**Warnings and Precautions:** Concomitant use with CYP3A substrates with narrow therapeutic ranges (e.g., alfentanil, fentanyl, and quinidine 1) may result in increases in the plasma concentrations of CYP3A substrates. Concomitant use with cyclosporine, tacrolimus, and sirolimus may result in increases in the plasma concentrations of cyclosporine, tacrolimus, and sirolimus.	**Serious Warnings and Precautions:** Leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure, and aplastic anemia. Potential teratogen and carcinogen	

CMV = cytomegalovirus; CYP3A = Cytochrome P4503A; dGTP = deoxyguanosine triphosphate; HSCT = hematopoietic stem cell transplant; IV = intravenous; R+ = cytomegalovirus-seropositive recipients.

[a] Health Canada–approved indication.

Source: Ganciclovir product monograph,[50] valganciclovir product monograph.[51]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of once daily letermovir (480 mg, administered orally or by IV, or 240 mg when co-administered with cyclosporine) for the prophylaxis of CMV infection in adult CMV-seropositive recipients of an allogeneic HSCT.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient Population	Adult CMV-seropositive recipients of an allogeneic HSCT **Subgroups:** • Age • Antiviral resistance • Risk of CMV infection (e.g., concomitant immunosuppressive therapy, antithymocyte globulin use, conditioning regimen, time since transplant, source of HSCT, donor serostatus, match and relation, GVHD, T-cell depletion, leukocyte antigen tissue match and relation, and haploidentical transplant)
Intervention	Letermovir 240 mg when co-administered with cyclosporine, or 480 mg once daily tablet or intravenous infusion
Comparators	Prophylaxis or pre-emptive antiviral therapy with any of the following agents: • Valganciclovir • Ganciclovir • Placebo
Outcomes	**Key efficacy outcomes:** • Clinically significant CMV infection • Initiation of PET • Mortality (e.g., all-cause, CMV-related) • Morbidity (e.g., CMV disease, end-stage organ disease) **Other efficacy outcomes:** • GVHD (acute, chronic) • Infections other than CMV • Hospitalization or re-hospitalization (e.g., all-cause, CMV-related) • Antiviral resistance (gene mutation) • Quality of life[a] **Harms outcomes:** • AEs • SAEs • WDAEs • Notable harms: gastrointestinal AEs, cardiac system AEs
Study Design	Published and unpublished phase III RCTs

AE = adverse events; CDR = CADTH Common Drug Review; CMV = cytomegalovirus; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; R+ = cytomegalovirus-seropositive recipients; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.
Note: Foscarnet and cidofovir were omitted from the review protocol given that they do not currently have Health Canada approval; however, it should be noted that cidofovir is available through special access in Canada. After consultation with the clinical expert for this CDR, both aciclovir and valacyclovir were also omitted from the review protocol, given that they do not have a Health Canada–approved indication for the treatment of CMV and because they are not commonly used to treat CMV in Canada.
[a] As measured by a validated scale.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases:

- MEDLINE (1946-) with in-process records and daily updates via Ovid
- Embase (1974-) via Ovid
- PubMed.

The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts were Prevymis and letermovir.

Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 11, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on September 20, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and contacts with appropriate experts. In addition, the drug manufacturer was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6.

Results

Findings from the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6. No studies were excluded based on full-text screening.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

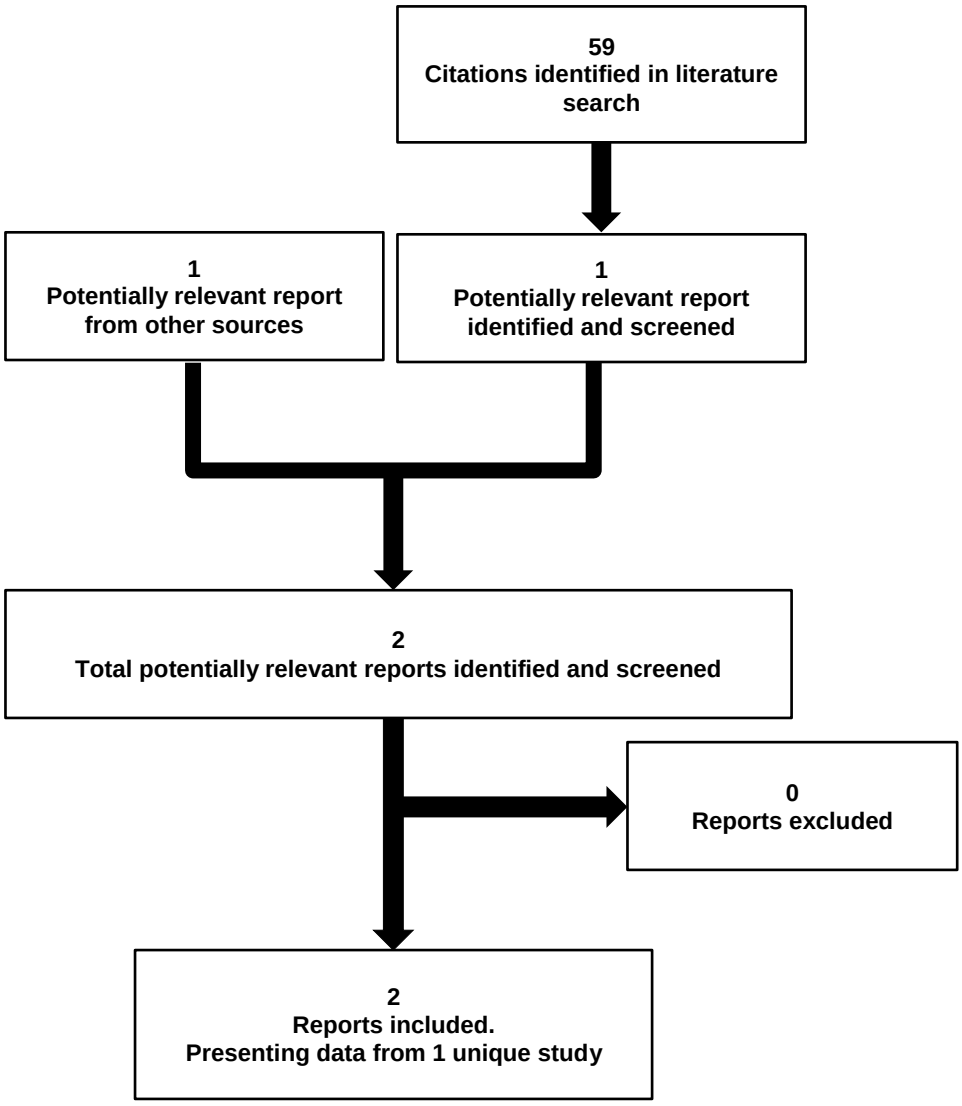


Table 6: Details of Included Studies

		Study P001
Designs and Populations	**Study Design**	DB, multi-centre, multinational, placebo-controlled, phase III RCT
	Locations	67 centres in 20 countries South America, Canada, Japan, South Korea, New Zealand, Romania, Turkey, US and Western Europe
	Randomized (N)	570
	Inclusion Criteria	• Adults with documented CMV-seropositive status within 1 year prior to HSCT • No more than 28 days post-HSCT at randomization • Undetectable CMV DNA from a plasma sample collected within 5 days prior to randomization

	Exclusion Criteria	• Received a previous allogeneic HSCT
		• History of CMV end-organ disease within 6 months prior to randomization
		• Received any of the following within 7 days prior to screening or planned to receive during the study:
		  ○ ganciclovir
		  ○ valganciclovir
		  ○ foscarnet
		  ○ acyclovir (at dosages > 3,200 mg PO per day or > 25 mg/kg per day
		  ○ valacyclovir (at dosages > 3,000 mg PO per day)
		  ○ famciclovir (at dosages > 1,500 mg PO per day)
		• Received within 30 days prior to screening or planned to receive during the study any of the following:
		  ○ cidofovir
		  ○ CMV hyperimmune globulin
		  ○ any investigational CMV antiviral agent / biologic therapy
		• Severe hepatic impairment (Child-Pugh score, Class C) within 5 days prior to randomization
		• Serum AST or ALT > 5 x ULN or serum total bilirubin > 2.5 x ULN within 5 days prior to randomization
		• End-stage renal impairment (creatinine clearance < 10 mL/min) within 5 days prior to randomization
		• Combination moderate hepatic impairment (Child-Pugh score, Class B) and moderate renal impairment (creatinine clearance < 50 mL/min)
		• Uncontrolled infection on the day of randomization
		• Required mechanical ventilation or was hemodynamically unstable at the time of randomization
		• Positive result for HIV-Ab test at any time prior to randomization, or HCV-Ab with detectable HCV RNA, or HBsAg within 90 days prior to randomization
		• Active solid tumour malignancies with the exception of localized basal cell or squamous cell skin cancer or the condition under treatment
		• Current or previous participation in a study with an unapproved investigational device (or compound) within 28 days (or 5 half-lives of initial dosage
		• Current, previous, or planned participation in a study involving CMV vaccine or another CMV investigational agent
		• Prior experience with letermovir
		• Current or recent history of drug or alcohol abuse or dependence

Drugs	**Intervention**	• Letermovir 480 mg oral tablet (or two 240 mg tablets) once daily no later than 28 days post-HSCT. • Letermovir 20 mg/mL (480 mg/vial) was also available as a once daily IV infusion (administered over one hour). • If co-administered with cyclosporine, the dosage of letermovir was to be reduced to 240 mg (240 mg tablet or 240 mg/vial IV solution) once daily.
	Comparator(s)	Matching placebo

		Study P001
Duration	**Phase**	
	Screening	Up to 15 days prior and up to 28 days post-transplant
	Treatment	14 weeks
	Follow-up	Up to 48 weeks (24 weeks for the primary end point)
Outcomes	**Primary End Point**	Incidence of clinically significant CMV through week 24 post-transplant defined as initiation of PET based on documented viremia and the clinical condition of the patient and/or CMV disease
	Secondary End Points	• Clinically significant CMV infection through week 14 post-transplant • Time to onset of clinically significant CMV infection through week 24 post-transplant • CMV disease through week 14 post-transplant and week 24 post-transplant • PET initiation for documented CMV viremia through week 14 post-transplant and week 24 post-transplant • Time to PET initiation for documented CMV viremia through week 24 post-transplant
	Other End Points	• CMV disease through week 48 post-transplant • All-cause mortality through weeks 14, 24, and 48 post-transplant • Infection (other than CMV) through weeks 14, 24, and 48 post-transplant • Acute and/or chronic GVHD through weeks 14, 24, and 48 post-transplant • All-cause re-hospitalization and/or for CMV infection/disease, weeks 14, 24, and 48 post-transplant • Antiviral resistance • Quality of life
Notes	**Publications**	Marty 2017[22]

ALT = alanine transaminase; AST = aspartate transaminase; CDR = CADTH Common Drug Review; CMV = cytomegalovirus; CSR = Clinical Study Report; DB = double-blind; GVHD = graft-versus-host disease; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCV-Ab = hepatitis C virus antibody; HIV-Ab = human immunodeficiency virus antibody; HSCT = hematopoietic stem cell transplant; IV = intravenous; min = minimum; N = total number in the sample under study; PET = pre-emptive therapy; PO = orally; RCT = randomized controlled trial; RNA = ribonucleic acid; ULN = upper limit of normal.

Source: CDR submission,[52] P001 V01 CSR,[23] P001 V02 CSR,[24] Marty 2017.[22]

Included Studies

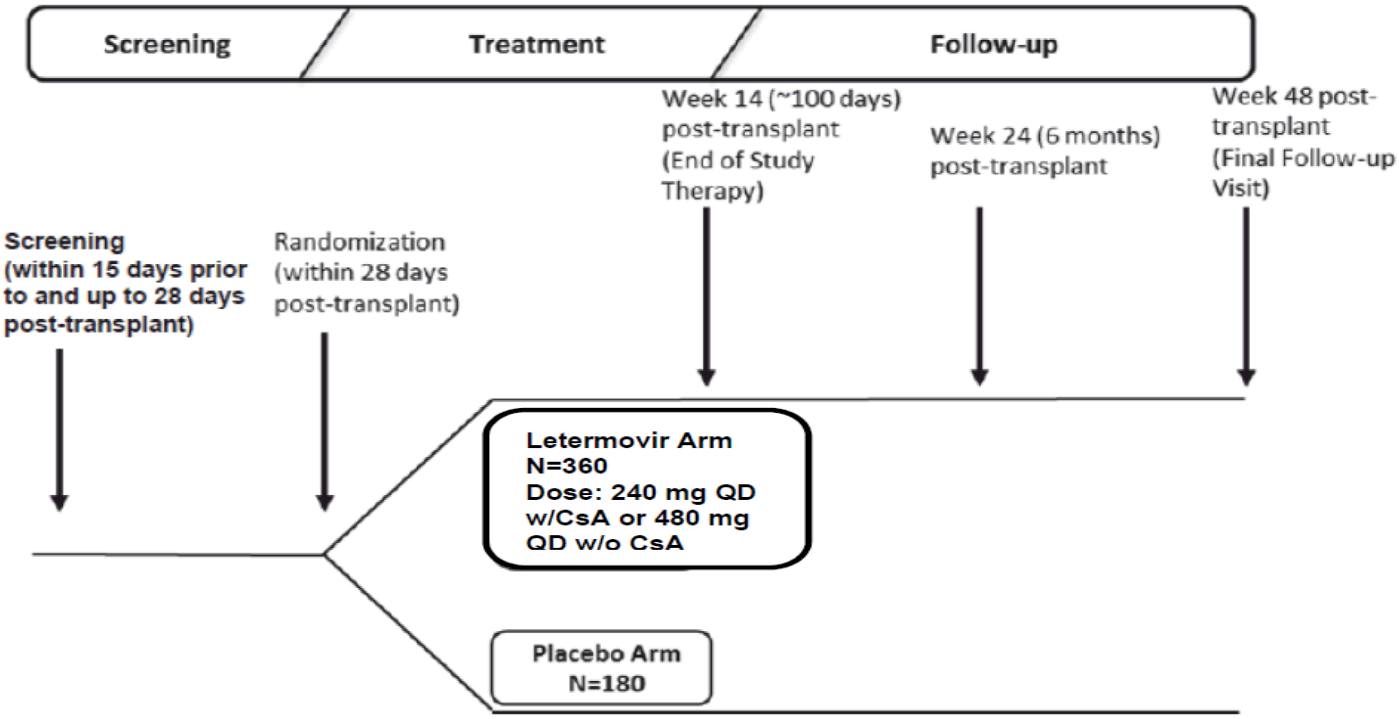
Description of Studies

Study P001 (N = 570) was a double-blind, multi-centre, multinational, placebo-controlled, phase III superiority randomized controlled trial. It recruited patients from centres located in North America (including Canada). The study objective was to evaluate the efficacy and safety of letermovir as a preventive strategy for clinically significant CMV infection in adults who are CMV-seropositive recipients of an allogeneic HSCT. Further details pertaining to the included study are provided in Table 6.

Patients could receive treatment up to 14 weeks post-transplant and were given follow-up to week 24 post-transplant for the primary and secondary end points. Subsequent to clinically significant CMV infection, patients were to continue to be followed in the trial (despite discontinuing study medication and initiating anti-CMV therapy) and complete all remaining trial visits. Data collection continued to week 48 post-transplant for the evaluation of exploratory outcomes. Once randomized to treatment, patients were monitored for CMV viremia weekly for the first 14 weeks post-transplant followed by biweekly monitoring thereafter through week 24 post-transplant. and every other month thereafter through week 48 post-transplant (given the reduced risk of CMV infection). A total of 431 (75.6%) patients continued the study beyond week 24 post-transplant.

Patients were allowed to withdraw from the trial at any time or could have been dropped from the trial at the investigator's discretion, had any untoward effects occurred. Details outlining the study design are provided in Figure 2.

Figure 2: Study P001 Design



CSR = Clinical Study Report; CsA = cyclosporine A; N = total number in the sample under study; QD = once daily; w/ = with; w/o = without.

Source: P001 V01 CSR.[23]

Populations

Inclusion and Exclusion Criteria

Study P001 enrolled adult patients with documented CMV-seropositive status within one year prior to HSCT. Patients were required to have undetectable CMV DNA from a plasma sample collected within five days prior to randomization and must have been enrolled within 28 days post-HSCT.

The following were all considered criteria for exclusion:

- a history of allogeneic HSCT
- CMV end-organ disease in the six months prior to randomization
- positive results for the HIV antibody test prior to randomization
- the hepatitis C virus antibody with detectable hepatitis C virus ribonucleic acid
- the hepatitis B surface antigen in the 90 days prior to randomization
- uncontrolled infection on the day of randomization
- severe hepatic impairment

- end-stage renal impairment in the five days prior to randomization
- moderate hepatic impairment combined with moderate renal impairment.

Patients were not enrolled if they received antiviral treatment with ganciclovir, valganciclovir, foscarnet, acyclovir, valacyclovir or famciclovir in the seven days prior to screening or planned to receive treatment with the latter during the study. Patients were also excluded if they received treatment with cidofovir, CMV hyperimmune globulin, or any investigational CMV antiviral agent / biologic therapy in the 30 days prior to screening, or planned to receive treatment with the latter during the study. Additional inclusion and exclusion criteria are detailed in Table 6.

Baseline Characteristics

Details of patients' baseline characteristics are presented in Table 7, Table 8, and Source: P001 V01 CSR23, Marty 2017.22

Table 9. Generally, the distributions of baseline patient characteristics were well balanced across treatment arms.

Patients enrolled in Study P001 had a mean age of 50.8 years (standard deviation 13.9), of whom the majority (68.0%) were between 36 and 64 years of age. Most enrolled patients were white (81.8%), male (57.9%) and located in Europe or North America (89.0%), and received HSCT less than two weeks prior to randomization (63.4%) (mean 11.5 days [standard deviation 8.5]).

The majority of patients enrolled in Study P001 were considered low risk for CMV infection (69.0%). A higher percentage of patients in the letermovir treatment arm were at higher risk of CMV infection compared with the placebo arm (32.4% in the letermovir arm and 28.1% in the placebo arm). Most patients were not engrafted at baseline (62.3%), were concomitantly treated with cyclosporine A (51.9%), received an HSCT from a CMV-seropositive donor (60.7%), and received a peripheral blood HSCT (73.1%). Overall, the letermovir treatment arm included more patients who received a peripheral blood HSCT compared with the placebo arm (74.8% in the letermovir arm and 69.8% in the placebo arm). The majority of patients did not have GVHD at baseline (99.3%), were treated with a myeloablative conditioning regimen (50.1%), and were previously treated with systemic antivirals (96.8%) — the most common being acyclovir (77.2%). The most common reason for HSCT was acute myeloid leukemia (37.9%) while the most common donor type was matched unrelated (38.6%). Overall, the letermovir treatment arm included more patients with myelodysplastic syndrome compared with the placebo arm (16.9% in the letermovir arm and 11.5% in the placebo arm).

Overall, a minority of patients received haploidentical HSCT (14.3%) or ex vivo T-cell depleted HSCT (2.5%), were concomitantly treated with alemtuzumab (4.1%) or antithymocyte globulin (35.0%). There were 7.3% fewer patients in the placebo arm (30.2%) compared with the letermovir arm (37.5%) who were treated with antithymocyte globulin and 5.2% fewer patients in the placebo arm (10.9%) compared with the letermovir arm (16.1%) who received an HSCT from a haploidentical donor.

Table 7: Summary of Baseline Characteristics

Characteristics	Study P001	
	Letermovir N = 373	Placebo N = 192
Age, years		
Mean (SD)	50.8 (13.4)	50.8 (14.8)
Median (min., max.)	53.0 (18.0, 75.0)	54.0 (18.0, 78.0)
18 to 35, n (%)	60 (16.1)	33 (17.2)
36 to 50, n (%)	103 (27.6)	49 (25.5)
51 to 64, n (%)	154 (41.3)	78 (40.6)
65 to 74, n (%)	55 (14.7)	30 (15 .6)
≥ 75, n (%)	1 (< 1)	2 (1.0)
Gender, n (%)		
Male	211 (56.6)	116 (60.4)
Race, n (%)		
Asian	40 (10.7)	18 (9.4)
Black or African	8 (2.1)	4 (2.1)
Multiracial	22 (5.9)	9 (4.7)
Native Hawaiian	1 (< 1)	0
White	301 (80.7)	161 (83.9)
Missing	1 (< 1)	0
Ethnicity, n (%)		
Hispanic or Latino	30 (8.0)	10 (5.2)
Not Hispanic or Latino	328 (87.9)	176 (91.7)
Not reported	6 (1.6)	5 (2.6)
Unknown	9 (2.4)	1 (0.5)
Geographical Region, n (%)		
Asia–Pacific	37 (9.9)	16 (8.3)
Latin America	7 (1.9)	2 (1.0)
Europe	185 (49.6)	97 (50.5)
North America	144 (38.6)	77 (40.1)
Body Weight, kg		
Mean (SD)	77.6 (18.0)	74.5 (15.9)
Median (min., max.)	76.2 (35.1, 141.5)	74.4 (40.9, 113.1)
Body Mass Index, kg/m^2		
Mean (SD)	26.5 (5.2)	25.5 (5.1)
Median (min., max.)	25.6 (17.0, 49.0)	25.1 (16.6, 44.7)
Days from Transplantation to Randomization		
Mean days (SD)	11.5 (8.5)	11.4 (8.6)
Median days (min., max.)	9 (0, 28)	9 (0, 28)
< 2 weeks, n (%)	237 (63.5)	121 (63.0)
≥ 2 weeks, n (%)	136 (36.5)	71 (37.0)

CSR = Clinical Study Report; max. = maximum; min. = minimum; N = total number in the sample under study; n = number in a subgroup of the sample under study; SD = standard deviation.

Source: P001 V01 CSR[23], Marty 2017.[22]

Table 8: Summary of Baseline Cytomegalovirus-Infection Risk Factors

Risk factors	Study P001	
	Letermovir N = 373	Placebo N = 192
CMV Infection Stratification,[a] n (%)		
High	121 (32.4)	54 (28.1)
Low	252 (67.6)	138 (71.9)
Engrafted at Baseline,[b] n (%)		
Yes	132 (35.4)	75 (39.1)
Not applicable	4 (1.1)	2 (1.0)
Immunosuppressive Regimen Use,[c] n (%)		
CsA	193 (51.7)	100 (52.1)
Tacrolimus	160 (42.9)	79 (41.1)
Other	19 (5.1)	10 (5.2)
Missing	1 (< 1)	3 (1.6)
CMV DNA detected on day 1	48 (12.9)	22 (11.5)
Primary Reason for HSCT, n (%)		
Acute lymphocytic leukemia	35 (9.4)	17 (8.9)
Acute myeloid leukemia	142 (38.1)	72 (37.5)
Aplastic anemia	9 (2.4)	11 (5.7)
Chronic lymphocytic leukemia	10 (2.7)	4 (2.1)
Chronic myeloid leukemia	17 (4.6)	6 (3.1)
Lymphoma	47 (12.6)	28 (14.6)
Myelodysplastic syndrome	63 (16.9)	22 (11.5)
Myelofibrosis	9 (2.4)	6 (3.1)
Plasma cell myeloma	14 (3.8)	10 (5.2)
Other	27 (7.2)	16 (8.3)
Donor CMV-serostatus, n (%)		
Positive	229 (61.4)	114 (59.4)
Unknown	5 (1.3)	0
Donor Type, n (%)		
Matched, related	127 (34.0)	64 (33.3)
Mismatched, related	57 (15.3)	22 (11.5)
Matched, unrelated	138 (37.0)	80 (41.7)
Mismatched, unrelated	51 (13.7)	26 (13.5)
Haploidentical related donor, n (%)	60 (16.1)	21 (10.9)
Antithymocyte globulin use, n (%)	140 (37.5)	58 (30.2)
Alemtuzumab use, n (%)	12 (3.2)	11 (5.7)
Ex vivo T-cell depletion, n (%)	9 (2.4)	5 (2.6)
Stem Cell Source, n (%)		
Peripheral blood	279 (74.8)	134 (69.8)
Bone marrow	82 (22.0)	47 (24.5)
Cord blood	12 (3.2)	11 (5.7)
Conditioning Regimen Use, n (%)		
Myeloablative	186 (49.9)	97 (50.5)
Reduced intensity conditioning	92 (24.7)	54 (28.1)
Non-myeloablative	95 (25.5)	41 (21.4)

Risk factors	Study P001	
	Letermovir N = 373	Placebo N = 192
Baseline Acute GVHD (≥ Grade 2)		
No	370 (99.2)	191 (99.5)
Missing	1 (< 1)	0

CMV = cytomegalovirus; CsA = cyclosporine A; CSR = Clinical Study Report; CsA = cyclosporine A; GVHD = graft-versus-host disease; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; N = total number in the sample under study; n = number in a subgroup of the sample under study.

[a] High risk is defined as patients meeting one or more of the following criteria at the time of randomization:

- 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
- grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥ 1 mg/kg/day of prednisone or equivalent dosage of another corticosteroid).

All patients not meeting definition of high risk were considered low risk.

[b] If the engraftment status at baseline was missing for a patient but an engraftment date was recorded later, the engraftment status at baseline was imputed to be no.

[c] Patients were counted in the CsA row if they received concomitant CsA with or without any other immunosuppressants during treatment phase. Tacrolimus containing-regimen included concomitant tacrolimus use with or without any other immunosuppressant use (except CsA). Patients in the other row received a regimen containing any other immunosuppressants (sirolimus, everolimus, systemic steroids, leflunomide, mycophenolate) except CsA or tacrolimus. The patients in the missing row did not receive any immunosuppressants concomitantly.

Source: P001 V01 CSR[23], Marty 2017.[22]

Table 9: Summary of Baseline Prior Medication

Prior Medication	Study P001	
	Letermovir N = 373	Placebo N = 192
Antivirals for Systemic Use, n (%)	365 (97.9)	182 (94.8)
Acyclovir	290 (77.7)	146 (76.0)
Valacyclovir hydrochloride	101 (27.1)	49 (25.5)
Antilymphocyte immunoglobulin, n (%)	132 (35.4)	58 (30.2)
Antivirals for HSV/VZV Prophylaxis, n (%)		
Acyclovir	311 (83.4)	152 (79.2)
Famciclovir	9 (2.4)	4 (2.1)
Valacyclovir	100 (26.8)	47 (24.5)

CSR = Clinical Study Report; HSV = herpes simplex virus; N = total number in the sample under study; n = number in a subgroup of the sample under study; VZV = varicella zoster virus.

Source: P001 V01 CSR[23], Marty 2017.[22]

Interventions

Randomization was conducted centrally using an interactive voice response system and integrated Web response system in a 2:1 ratio (letermovir: placebo); it was stratified by trial centre and risk for CMV infection to mitigate any confounding associated with these factors.

Study P001 used a double-blind treatment concealing assignments to blind patients, investigators, and sponsor personnel who were involved in the treatment or clinical evaluation of the patients. Letermovir tablets were packaged identically to matching placebo so that blinding was maintained. Intravenous letermovir, or matching IV placebo, were prepared in a blinded fashion by an unblinded pharmacist (or qualified trial site personnel),

using opaque covers for the IV bags in order to ensure the blinding of study medication. The pharmacist was not involved in evaluation of patient response or safety.

Initially, only 240 mg tablets were available. The protocol was subsequently amended, introducing 480 mg tablets, making both the 240 mg and 480 mg tablets of letermovir available. Patients enrolled after the protocol amendment who required the oral 480 mg dose were initiated with one 480 mg tablet (letermovir or matching placebo). In the event a patient was unable to swallow the 480 mg tablet, study medication could be initiated with two 240 mg tablets (letermovir or matching placebo). Patients who were initiated with two 240 mg letermovir tablets or matching placebo prior to the protocol amendment continued with that regimen. If the 480 mg tablet was not available in a country based on country-specific requirements, two 240 mg tablets were used as an alternative.

Letermovir was administered at a dosage of 480 mg once daily (adjusted to 240 mg when co-administered with cyclosporine A) or matching placebo, with or without food, at approximately the same time each day, and was available in both oral and IV formulations with no dose adjustments. If cyclosporine A was initiated after letermovir (or matching placebo), the next dosage of letermovir (administered up to 24 hours later) was reduced to 240 mg once daily. If cyclosporine A was discontinued after treatment with letermovir (or matching placebo) was initiated, the next dosage of treatment (administered up to 24 hours later) was to be increased to 480 mg once daily. If concomitant cyclosporine A was temporarily adjusted, no letermovir dose adjustments were required.

The availability of the IV formulation of letermovir allowed treatment to be initiated as early as the day of HSCT in patients who could not tolerate oral intake. Patients were administered oral formulation of study medication, provided they were able to swallow and did not have a condition (e.g., vomiting, diarrhea, or a malabsorptive condition) that interfered with the absorption of the tablets. Otherwise, the IV formulation was administered until such time that patients were able to swallow and/or the condition necessitating the use of the IV formulation resolved. Investigators were given the option to randomize patients to treatment up to 28 days post-transplant and continue treatment through week 14 post-transplant (the period of highest risk for CMV infection and/or disease in HSCT recipients). The duration of treatment for an individual patient varied from 10 to 14 weeks post-transplant, given that patients could be randomized to treatment at any time over a four-week period after HSCT. All patients were to complete treatment at the same time point post-transplant — week 14 post-transplant.

Missed treatment dosages were to be taken as soon as possible on the same day, unless more than 18 hours had elapsed since the previous dosage. Otherwise, the missed dosage was to be skipped and the original dosing schedule to be resumed. Doses were not to be doubled to compensate for missed treatment dosages.

The following therapies were permitted during Study P001:

- standard antimicrobial prophylaxis (e.g., levofloxacin for bacteria, fluconazole/posaconazole for fungi)
- acyclovir, valacyclovir, or famciclovir for prophylaxis and treatment of herpes simplex virus or varicella zoster virus infections at doses no greater than prohibited doses of the medications detailed in the next paragraph
- all types of prior conditioning regimens (including myeloablative, reduced intensity, or non-myeloablative regimens)

- prior or ongoing graft manipulation regimens (including various ex vivo or in vivo T-cell depletion or selection regimens)
- GVHD prophylaxis regimens
- mycophenolate mofetil.

Antiviral drugs or therapies for the management of CMV, including but not limited to the following, were prohibited during study P001:

- ganciclovir
- valganciclovir
- foscarnet
- cidofovir
- acyclovir at dosages > 3,200 mg oral per day or > 25 mg/kg IV per day
- valacyclovir at dosages > 3,000 mg oral per day
- famciclovir at dosages > 1,500 mg oral per day
- CMV hyperimmune globulin
- any investigational CMV antiviral agent / biologic therapy, including CMV vaccines. Investigational agents were not permitted, except for the following: investigational chemotherapy regimens involving approved agents and investigational antimicrobial regimens involving approved antibacterial / antifungal / antiviral agents.

Outcomes

Efficacy

Primary Outcome

The primary efficacy end point in Study P001 was the incidence of clinically significant CMV infection through week 24 post-transplant. Clinically significant CMV infection was defined as:

- occurrence of CMV end-organ disease or
- initiation of PET, based on documented CMV viremia and the clinical condition of the patient.

For CMV end-organ disease (also considered a secondary end point), suspected cases reported by the investigators were reviewed by an independent blinded clinical adjudication committee. The clinical adjudication committee confirmed the suspected cases of CMV end-organ disease and diagnosis based on clinical, virological, and histopathological data, as well as diagnostic data if applicable. All personnel involved in the adjudication process, including the clinical adjudication committee, remained blinded to treatment allocation throughout the trial. Only the clinical adjudication committee–confirmed cases of CMV end-organ disease were included in the CMV end-organ disease category. However, investigator–assessed CMV end-organ disease cases that were not confirmed by the committee but in which anti-CMV therapy was initiated (based on documented CMV viremia at a central laboratory) were included in the initiation-of-PET category and, therefore, qualified as having clinically significant CMV infection.

For the initiation of PET based on documented viremia (also considered a secondary end point), the criteria for documented viremia was defined as any detectable CMV viral DNA on a confirmatory sample (from a central laboratory) obtained immediately prior to the initiation

of treatment for CMV disease or PET. Detectable CMV viral DNA includes reporting of PCR results as detected but not quantifiable, or detected with a numeric value. If an affirmative result obtained on the day of PET initiation was not available, a subsequent sample had to be obtained and sent to the central laboratory within seven days after initiation of PET. In the event test results from the central laboratory were not available within seven days post-PET initiation, the investigator could use a positive local laboratory test (CMV DNA PCR or pp65 antigen only).

Although specific thresholds for initiating PET were not mandated per-protocol (PP) — as a patient's risk status and clinical condition may have changed during the course of the trial and was best assessed by the investigator taking care of the patient — protocol-recommended viral load thresholds for the initiation of PET based on the risk groups derived from standard practice at the Fred Hutchinson Cancer Research Center and from the Roche Cobas AmpliPrep/Cobas TaqMan (CAP/CTM) assay, the current international standard for measuring CMV DNA. The thresholds were as follows.

Through week 14 post-transplant:

- high risk – viral DNA ≥ 150 copies/mL
- low risk – viral DNA > 300 copies/mL.

Beyond week 14 post-transplant:

- high risk – viral DNA > 300 copies/mL
- low risk – viral DNA > 300 copies/mL.

CMV viremia was assessed by PCR using the Roche CAP/CTM assay (Appendix 5) with a lower limit of quantification of 137 IU/mL, or approximately 150 copies/mL based on a conversion factor of 1.1 copies/IU as per the assay package insert. Where an affirmative test result was not available, a subsequent central laboratory result was collected from a sample obtained within seven days of initiating anti-CMV agents, and used instead. Initiation of anti-CMV therapy without documented CMV viremia (using the central laboratory) was not considered as a case of clinically significant CMV infection. Similarly, depending on the clinical condition of the patient, detectable CMV viral DNA alone without the initiation of anti-CMV therapy was not considered to be a case of clinically significant CMV infection. Details regarding the assessment of the clinical condition of the patient were not provided. The antivirals considered for PET were ganciclovir, valacyclovir, foscarnet, and/or cidofovir.

PET and CMV end-organ disease were considered as separate end point events if PET was initiated more than two weeks prior to the onset of adjudicated CMV end-organ disease. If PET was initiated in the two weeks prior to or after the onset of adjudicated CMV end-organ disease, then PET was not counted as an end-point event.

Secondary Outcomes

Secondary efficacy outcomes were considered supportive and included the following.

- **The proportion of patients with clinically significant CMV infection through week 14 post-transplant:** For this end point, case counting used the same definition as in the primary efficacy end point.
- **The time to onset of clinically significant CMV infection through week 24 post-transplant:** For individual events, it was relative to the start of transplantation to the onset of the respective event.

- **The proportion of patients with CMV disease through week 14 post-transplant and week 24 post-transplant:** For this end point, case counting used the same definition for CMV end-organ disease as in the primary efficacy end point.
- **The proportions of patients with initiation of PET for documented CMV viremia through week 14 post-transplant and week 24 post-transplant:** For this end point, case counting used the same definition for initiation of PET for documented CMV viremia as in the primary efficacy end point.
- **The time to initiation of PET for documented CMV viremia through week 24 post-transplant:** The time to initiation of PET for documented CMV viremia was calculated in days — from the day of randomization to the start date of anti-CMV therapy. Included were applicable cases where CMV end-organ disease was not confirmed by the clinical adjudication committee.

Exploratory Outcomes

All-cause mortality was defined as patients who died for any reason while in the study, whereas non-relapse mortality was defined as death due to any reason other than the primary condition for which a HSCT was performed. A post hoc analysis of CMV-related mortality (defined as death due to any reason in patients with clinically significant CMV infection) was performed to provide additional information related to the all-cause mortality end point.

Opportunistic infection was considered to be any infection that, in the opinion of the investigator, would be considered an opportunistic infection in the HSCT setting (e.g., serious bacterial or invasive fungal infections, Epstein-Barr post-transplant lymphoproliferative disease, respiratory syncytial virus, pneumonia, parainfluenza pneumonia, adenovirus disease, Pneumocystis jiroveci pneumonia, human herpesvirus 6 encephalitis, and toxoplasmosis.)

The Glucksberg grading system was used by investigators for grading of acute GVHD in Study P001. No grading was required for chronic GVHD as there were several grading systems used and the prognostic value of these scales was not well defined. GVHD was considered to be acute if it occurred prior to day 100 post-transplant or if a grade was provided after day 100 post-transplant. In contrast, GVHD was considered to be chronic if it occurred after day 100 post-transplant or if no grade was provided prior to day 100 post-transplant.

Re-hospitalization was defined as hospitalization for any reason following initial hospital discharge, whereas re-hospitalization for CMV infection / disease was defined as hospitalization for CMV infection / disease following initial hospital discharge.

Two questionnaires, the 3-level version of EuroQol 5-Dimensions (EQ-5D-3L) and the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT), version 4, are validated tools of patient reported outcomes that were also evaluated in Study P001 (Appendix 4).

The EuroQol 5-Dimensions (EQ-5D) is a generic health-related quality of life instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing no problems, some problems, and extreme problems, respectively. Index

scores less than zero represent health states that are valued by society as being worse than dead, while scores of zero and 1.00 are assigned to the health states labelled 'dead' and 'perfect health,' respectively. The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled zero and 100, with respective anchors of worst imaginable health state and best imaginable health state. Although the minimum clinically important difference (MCID) for the EQ-5D in CMV-seropositive recipients of an allogeneic HSCT remains unclear, differences of 0.033 to 0.074 in the index score are typically clinically meaningful in other conditions.

FACT-BMT is a self-assessment tool that is used to measure the quality of life in patients who have received either an autologous or allogeneic HSCT performed to treat an underlying hematological condition. The FACT-BMT comprises 47 questions, scored on a scale from zero to 164 measuring the following domains: physical well-being, social or family well-being, emotional well-being, functional well-being, and additional concerns related to the patient's clinical condition. The items are scored on a Likert-type scale, which ranges from zero to four (zero = not at all, one = a little bit, two = somewhat, three = quite a bit, four = very much). The FACT-BMT includes both subscale scores and individual scores, with higher scores indicating better quality of life. Although the MCID for the FACT-BMT in CMV-seropositive recipients of an allogeneic HSCT remains unclear, differences of three to seven for the FACT-G (parent questionnaire of the FACT-BMT) are typically clinically meaningful in other conditions.

The potential for viral resistance in patients who received letermovir was evaluated by CMV DNA sequence analysis. Plasma collected during a CMV infection visit (occurring when an investigator intended to initiate either treatment for CMV disease or PET) was analyzed for CMV genotypic variants (GVs) using validated protocols performed by established contract laboratories. In patients with multiple CMV infection visits, all samples were tested; however, the sample closest to the last dosage of study medication with DNA sequence results for UL56 and/or UL89 was used for the primary genotyping analysis. Although CMV genotyping was performed regardless of study medication (letermovir or placebo), phenotypic analysis of GVs was only to be performed on variants that had not been previously characterized from patients who received letermovir. The potential for resistance to letermovir was assessed by genotypic analysis of the CMV terminase complex genes UL56 and UL89. The DNA sequence of the protein-coding regions of UL56 and UL89 was determined, and deduced amino acid sequences were aligned with the corresponding UL56 and UL89 amino acid sequences from the letermovir susceptible Merlin reference strain.

Harms

AEs were defined as any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with treatment. An AE can therefore have been any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of the drug was also considered an AE.

Serious AEs were defined as any adverse experience occurring at any dosage or during any use of the drug that resulted in death, was life-threatening, resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing inpatient hospitalization, was considered a congenital anomaly or birth defect, other important

medical event, cancer, or was associated with an overdose defined as any dose higher than twice the specified dose.

Withdrawal due to AEs was defined as patient withdrawal from the trial at any time or discontinuation from the trial at the discretion of the investigator, should any untoward effects have occurred.

Statistical Analysis

Sample Size and Power

Study P001 was designed to assess the effect of letermovir using clinically significant CMV infection as the primary end point. Based on available literature and on the results from the phase II trial, the incidence rate of clinically significant CMV infection through week 24 post-transplant for patients receiving placebo was anticipated to be approximately 35%.[13] It was also anticipated that letermovir would reduce this incidence by half (approximately 17%). It was further anticipated that about 20% of patients would be discontinued from the trial from both treatment arms for reasons other than virologic failure. Given that the primary analysis comprised an approach by which missing data were imputed, 20% for missing outcomes was added to the expected incidence of clinically significant CMV infection for the placebo arm (55%) and the letermovir arm (37%) for sample size and power calculations. Therefore, a sample size of approximately 540 patients was planned using a 2:1 randomization ratio (approximately 360 patients in the letermovir arm and approximately 180 patients in the placebo arm). With this sample size, the trial had at least 90.5% power to detect a treatment difference with a one-sided *P* value less than or equal to 0.0249. Of note, Study P001 had one interim futility analysis when approximately 40% of the patients had completed the treatment regimen, and for which alpha = 0.0001 was the power cost.

Primary End Point

Primary Analysis

The primary analysis of the primary end point was conducted in the full analysis set (FAS) population using stratum-adjusted Mantel–Haenszel methods (with continuity correction) stratified by risk for CMV infection (high versus low risk). Due to the large number of study centres, ‘centre’ was not included as a stratification factor in the primary analysis. All non-completers (patients who prematurely discontinued from the study) and patients with any missing values were treated as having experienced the primary end point event. A patient who discontinued study medication but remained in the study follow-up was not considered a non-completer. Cochran–Mantel–Haenszel weights were used to calculate the overall between-group differences across strata. Data are presented as mean difference in the change from baseline compared with placebo with corresponding 95% confidence intervals (CI). Letermovir was to be considered superior to placebo if the one-sided *P* value was less than or equal to 0.0249.

Sensitivity Analyses

Sensitivity analyses were also performed for the primary end point and were analyzed in a similar manner (stratum-adjusted Mantel–Haenszel methods) and included:

- data as observed, where any patient with a missing value for a particular end point was excluded from the analysis
- PP population
- data missing at random and data not missing at random approaches

- only patients who had detectable CMV viral DNA on day 1.

Subgroup Analyses

The treatment effect on the primary efficacy end point was also evaluated within each of the following pre-specified subgroups:

- age (use median age cut-off, ≥ 65 years, < 65 years)
- weeks from HSCT to randomization (< two weeks, ≥ two weeks)
- high and low risk of CMV infection
- ex vivo T-cell depletion (yes, no)
- alemtuzumab use (yes, no)
- stem cell source (peripheral blood, bone marrow, cord blood)
- GVHD ≥ grade 2 (yes, no)
- donor human leukocyte antigen–matching and relation (matched, related; mismatched, related; matched, unrelated; mismatched, unrelated)
- haploidentical (yes, no)
- conditioning regimen (myeloablative, reduced intensity, non-myeloablative)
- immunosuppressant use (cyclosporine A, tacrolimus, other).

Of note, subgroup analyses were not performed for subcategories with fewer than 20 patients in the letermovir group or fewer than 10 patients in the placebo group. In such cases, only descriptive statistics were provided.

Subgroup analyses were performed in the FAS population and were analyzed in a similar manner to the primary end point (stratum-adjusted Mantel–Haenszel methods in the FAS population, treating non-completers and any missing values as having experienced the primary end points). Furthermore, only the data-as-observed sensitivity analysis was performed for the primary end point in subgroups. Overall, none of the subgroup analyses were adjusted for multiple statistical tests. Randomization was not stratified for any of the pre-specified subgroups with the exception of high and low risk for CMV infection.

Secondary End Points

Secondary efficacy analyses were assessed in a similar manner to the primary end point (stratum-adjusted Mantel–Haenszel methods in the FAS population treating non-completers and any missing values as having met the primary end point) with the exception of time-to-event analyses, which used non-parametric Kaplan–Meier methods and stratified log-rank test to provide *P* values. No adjustments were made to control for type I error.

A summary of the analysis strategies for the efficacy end point in Study P001 are provided in Table 10.

Table 10: Summary of Analysis Strategies for Primary and Secondary Efficacy End Points in Study P001

End Point	Primary vs. Sensitivity Approach	Statistical Method	Analysis Population	Missing Data Approach	Type I Error Correction
Primary End Point					
Proportion of patients with clinically significant CMV infection through week 24 post-transplant	Primary	Stratified M & H	FAS	NC = F	NA
	Sensitivity	Stratified M & H	PP	NC = F	No
	Sensitivity	Stratified M & H	FAS	DAO	No
Secondary End Points					
Proportion of patients with clinically significant CMV infection through week 14 post-transplant	Primary	Stratified M & H	FAS	NC = F	No
	Sensitivity	Stratified M & H	PP	NC = F	No
	Sensitivity	Stratified M & H	FAS	DAO	No
Time to onset of clinically significant CMV infection through week 24 post-transplant	Primary	Non-parametric Kaplan–Meier plot[a]	FAS	Censored at last assessment	No
Proportion of patients with CMV disease through week 14 post-transplant and 24 post-transplant	Primary	Stratified M & H	FAS	NC = F	No
	Sensitivity	Stratified M & H	PP	NC = F	No
	Sensitivity	Stratified M & H	FAS	DAO	No
Proportion of patients with initiation of PET for documented CMV viremia through week 14 post-transplant and 24 post-transplant	Primary	Stratified M & H	FAS	NC = F	No
	Sensitivity	Stratified M & H	PP	NC = F	No
	Sensitivity	Stratified M & H	FAS	DAO	No
Time to initiation of PET for documented CMV viremia through week 24 post-transplant	Primary	Non-parametric Kaplan–Meier plot[a]	FAS	Censored at last assessment	No

CMV = cytomegalovirus; CSR = Clinical Study Report; DAO = data as observed; FAS = full analysis set; M & H = Mantel–Haenszel; NC= F = non-completers equals failure; *P* = probability; PET = pre-emptive therapy; PP = per-protocol.

Note: Sensitivity analyses are referred to as supportive analyses by the manufacturer. The Mantel–Haenszel method was stratified by high and low risk factors.

[a] *P* value provided using stratified log-rank test.

Source: P001 V01 CSR.[23]

Exploratory End Points

Only summary statistics were provided by treatment arm for exploratory end points through weeks 14, 24, and 48 post-transplant.

The results of the quality of life data analyses were only performed at week 48 post-transplant. Standard algorithms were used to compute total and subscale scores for the FACT-BMT version 4 and EQ-5D-3L questionnaires as specified by the instrument developers. Given that Study P001 was not powered to detect statistically significant differences in quality of life scores between the treatment arms, the analysis plan was primarily descriptive and exploratory in nature. Questionnaire data were summarized using descriptive statistics at each administration time point by treatment arm with no imputations for missing data.

Harms

Proportions of patients with at least one AE, drug-related AEs, serious AEs, serious drug-related AEs, and an AE leading to discontinuation were summarized and compared between treatment arms using summary statistics. For safety end points, all analyses were based on the observed data (with no imputation of missing data) and based on all patients as treated population. All AEs were collected through 14 days after completion of treatment

period. Thereafter, any serious AEs related to study medication or serious AEs leading to death were collected through week 48 post-transplant.

Analysis Populations

Efficacy data were analyzed in the following populations:

- The FAS population served as the primary population for the analysis of efficacy data Study P001. The FAS consisted of all randomized patients who received at least one dosage of study medication and had no detectable CMV viral DNA (measured by the central laboratory) on day 1 (when study medication was initiated).
- Supportive analyses using the PP population were performed for the primary and key secondary efficacy end points. The PP population was defined as a subset of the FAS population and excluded patients due to important deviations from the protocol that may substantially affect the results of the primary and key secondary efficacy end points. Potential violations that may have resulted in the exclusion of a patient from the PP population included:
  - failure to reasonably adhere to the dosing schedule for the study medication
  - failure to meet specific inclusion or 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 was made prior to the unblinding of the database.

Patients were included in the treatment arm to which they were randomized for the analysis of efficacy data using both the FAS and PP populations.

The all-patients-as-treated population was used for the analysis of safety data in this study. The all-patients-as-treated population consisted of all randomized patients who received at least one dosage of study medication. Patients were included in the treatment arm corresponding to the study medication that they actually received for the analysis of safety data using the all-patients-as-treated population. At least one laboratory or vital sign measurement obtained subsequent to at least one dosage of study medication was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

Patient Disposition

Of the 738 patients screened in Study P001, approximately 23% did not meet the criteria for enrolment. The most common reasons for the 168 screening failures were evidence of CMV viremia prior to randomization (84 patients), followed by detectable CMV DNA (as confirmed by the central laboratory) from a plasma sample collected in the five days prior to randomization (59 patients). The majority of patients completed the study through week 24 post-transplant (approximately 76%) and beyond week 48 post-transplant (approximately 64%). Generally, more patients discontinued the study in the placebo arm compared with the letermovir arm through week 24 post-transplant (28.9% compared with 20.7%, respectively), while fewer patients discontinued the study in the placebo arm compared with the letermovir arm between weeks 24 and 48 post-transplant (8.8% compared with 13.6%, respectively). The most common reason for discontinuation through both week 24 post-transplant and week 48 post-transplant was death (11.4% and 8.8%, respectively). Overall, a similar number of patients discontinued the study due to AEs in both groups.

More patients discontinued treatment in the placebo arm compared with the letermovir arm (57.7% compared with 28.2%, respectively). The most common reason for discontinuation of treatment was due to lack of efficacy (42.3% in the placebo group compared with 6.4% in the letermovir group). Details about patient disposition in Study P001 are provided in Table 11.

Table 11: Patient Disposition

Disposition	Study P001	
	Letermovir	Placebo
Screened, n	738	
24 Weeks Post-Transplant		
Randomized, n (%)	376	194
Not treated	3 (< 1)	2 (1.0)
Completed through week 24 post-transplant	295 (78.5)	136 (70.1)
Discontinued Study Through 24 Weeks Post-Transplant, n (%)	78 (20.7)	56 (28.9)
Adverse event	6 (1.6)	3 (1.5)
Death	37 (9.8)	28 (14.4)
Lost to follow-up	2 (0.5)	4 (2.1)
Non-compliance with study drug	1 (0.3)	0
Physician decision	9 (2.4)	5 (2.6)
Withdrawal by patient	23 (6.1)	16 (8.2)
Discontinued Treatment Through 24 Weeks Post-Transplant, n (%)	106 (28.2)	112 (57.7)
Adverse event	42 (11.2)	19 (9.8)
Death	5 (1.3)	4 (2.1)
Prohibited concomitant medication	3 (0.8)	0
Lack of efficacy	24 (6.4)	82 (42.3)
Non-compliance with study drug	5 (1.3)	1 (0.5)
Physician decision	7 (1.9)	2 (1.0)
Withdrawal by patient	20 (5.3)	4 (2.1)
FAS,[a] n (%)	325 (86.4)	170 (87.6)
PP, n (%)	295 (78.5)	156 (80.4)
ASaT, n (%)	373 (99.2)	192 (99.0)
Beyond 24 Weeks Post-Transplant		
Entered, n (%)	295 (78.5)	136 (70.1)
Completed through week 48 post-transplant, n (%)	244 (64.9)	119 (61.3)
Discontinued Study Between 24 and 48 Weeks Post-Transplant, n (%)	51 (13.6)	17 (8.8)
Death	34 (9.0)	16 (8.2)
Lost to follow-up	6 (1.6)	0
Physician decision	6 (1.6)	0
Withdrawal by patient	5 (1.3)	1 (0.5)

ASaT= all patients as treated; CMV = cytomegalovirus; CSR = Clinical Study Report; FAS = full analysis set; n = number in a subgroup of the sample under study; PP = per-protocol.

[a] Excludes 48 and 22 patients in the letermovir and placebo groups, respectively, due to detectable CMV DNA on day 1, respectively.

Source: P001 V01 CSR,[23] P001 V02 CSR,[24] Marty 2017.[22]

Exposure to Study Treatments

The majority (98.4%) of patients in the letermovir treatment arm received the oral tablet formulation in Study P001 (mean exposure 61 days), of which approximately half (50.6%) received treatment for 10 to 14 weeks. Furthermore, approximately half (52.0%) of the

patients were treated with the 240 mg oral dose due to concomitant immunosuppressive therapy with cyclosporine A. Approximately one-quarter (26.5%) of patients were treated with intravenous formulation of letermovir (mean exposure 13.5 days), of which 15.8% received treatment for ≤ two weeks. Details about exposure in Study P001 are provided in Table 12.

Overall, mean (standard deviation) compliance to treatment was 98.2% (5.7) in Study P001, in which the majority of patients were 100% compliant (approximately 80% of patients). Details about treatment compliance in P001 are provided in Table 13.

Approximately 98% of patients were treated with concomitant antiviral therapies for systemic use through week 14 post-transplant (treatment phase), the most common being acyclovir (75.4%). The majority of patients were also treated with immunosuppressive therapy through week 14 post-transplant (approximately 98%), of which the most common types were cyclosporine A and tacrolimus (51.9% and 46.0%, respectively). Overall, 4.1% and 34.7% of patients were treated with concomitant alemtuzumab and antithymocyte globulin, respectively. Details about concomitant medications in Study P001 are provided in Table 14.

Table 12: Summary of Treatment Exposure

Exposure	Study P001					
Mode of Administration	IV		PO			Any
Dose	240 mg	480 mg	240 mg	480 mg	960 mg	Any
Letermovir						
Exposure, mean days (SD)	13.6 (NR)	13.5 (NR)	62.2 (NR)	60.6 (NR)	3.0 (NR)	69.4 (NR)
Exposure, median days (min., max.)	12 (1, 45)	12 (1, 47)	77 (1, 105)	71 (1, 109)	3 (3, 3)	82 (1, 113)
Duration of exposure, n						
≤ 2 weeks	23	36	37	34	1	47
> 2 to 4 weeks	11	26	9	16	0	22
> 4 to 6 weeks	2	3	7	7	0	10
> 6 to 8 weeks	1	1	11	10	0	12
> 8 to 10 weeks	0	0	22	32	0	30
> 10 to 12 weeks	0	0	39	55	0	84
> 12 to 14 weeks	0	0	60	35	0	132
≥ 14 weeks	0	0	9	16	0	36
Placebo						
Exposure, mean days (SD)	13.2 (NR)		53.2 (NR)			55.2 (NR)
Exposure, median days (min., max.)	12 (1, 88)		54 (1, 112)			56 (4, 115)
Duration of exposure, n						
≤ 2 weeks	31		34			27
> 2 to 4 weeks	16		22			29
> 4 to 6 weeks	0		26			27
> 6 to 8 weeks	0		12			15
> 8 to 10 weeks	0		17			13
> 10 to 12 weeks	0		38			33
> 12 to 14 weeks	1		27			33
≥ 14 weeks	0		11			15

CSR = Clinical Study Report; IV = intravenous; max. = maximum; min. = minimum; n = number in a subgroup of the sample under study; NR = not reported; PO = orally; SD = standard deviation.

Source: P001 V01 CSR.[23]

Table 13: Summary of Treatment Compliance

Compliance	Study P001	
	Letermovir N = 373	Placebo N = 192
Mean % (SD)	98.2 (5.7)	98.3 (5.5)
Median (min., max.)	100 (57.0 to 100)	100 (66.7 to 100)
Treatment compliance, n (%)		
< 75%	9 (2.4)	4 (2.1)
≥ 75% to < 90%	8 (2.1)	8 (4.2)
≥ 90% to <100%	71 (19.0)	20 (10.4)
100%	285 (76.4)	160 (83.3)

CSR = Clinical Study Report; max. = maximum; min. = minimum; N = total number in the sample under study; n = number in a subgroup of the sample under study; SD = standard deviation.

Source: P001 V01 CSR.[23]

Table 14: Summary of Concomitant Medication Through Week 14 Post-Transplant

Concomitant Medication, n (%)	Study P001	
	Letermovir N = 373	Placebo N = 192
Antivirals for Systemic Use	364 (97.6)	188 (97.9)
Acyclovir	287 (76.9)	139 (72.4)
Foscarnet sodium	20 (5.4)	20 (10.4)
Ganciclovir	13 (3.5)	34 (17.7)
Valacyclovir hydrochloride	125 (33.5)	60 (31.3)
Valganciclovir hydrochloride	16 (4.3)	45 (23.4)
Globulin, immune	65 (17.4)	32 (16.7)
Immunosuppressive Regimen Use	366 (98.1)	187 (97.4)
Cyclosporine A	193 (51.7)	100 (52.1)
Tacrolimus	174 (46.6)	86 (44.8)
Everolimus	7 (1.9)	3 (1.6)
Mycophenolate mofetil	123 (33.0)	55 (28.6)
Sirolimus	36 (9.7)	27 (14.1)
Systemic corticosteroids	246 (66.0)	122 (63.5)
Alemtuzumab	12 (3.2)	11 (5.7)
Antithymocyte globulin	138 (37.0)	58 (30.2)

CSR = Clinical Study Report; N = total number in the sample under study; n = number in a subgroup of the sample under study.

Source: P001 V01 CSR.[23]

Critical Appraisal

Internal Validity

Study P001 was designed as a double-blind, placebo-controlled randomized controlled trial that used appropriate methods to randomize patients (interactive voice and integrated Web response systems) and appropriate methods to conceal treatment allocation. The objective of Study P001 was to assess the efficacy and safety of letermovir administered prophylactically, based on a primary end point of clinically significant CMV infection (defined as initiation of PET based on documented viremia and the clinical condition of the patient or CMV end-organ disease).

Randomization was stratified by two variables: risk for CMV infection and study centre. The latter was not included as a stratification factor in the primary efficacy analysis due to the large number of study centres. Guidance from the European Medicines Agency suggests that both adjusting for study centres and not adjusting for study centres in the primary efficacy analysis may lead to unreliable estimates of the treatment effect and *P* values. Sensitivity analyses that adjusted for study centres in the analysis are recommended and would have been helpful to ensure that trial conclusions are not substantially affected; however, these types of analyses were not performed.[53]

Study P001 was designed as a superiority trial against placebo and, therefore, analyses should ideally be conducted in an intention-to-treat population. However, all efficacy analyses were conducted using the FAS population defined as all randomized patients who received at least one dosage of study medication and had no detectable CMV viral DNA (measured by the central laboratory) on day 1 (when study medication was initiated). The exclusion of patients with detectable CMV viral DNA on day 1 is inconsistent with the true definition of an intention-to-treat population analysis, in which all randomized participants are included.

In the stratum-adjusted Mantel–Haenszel method used in the primary analysis, missing data were imputed by which all non-completers and any missing values were considered as having met the primary end point (non-completers is the term referring to patients who prematurely discontinued taking part in the study; patients who discontinued study medication but remained in the study follow-up were not considered non-completers). To assess the robustness of the treatment effect, multiple sensitivity analyses were conducted using different methods to impute missing data.

The criteria for initiating PET based on documented viremia was defined as any detectable CMV viral DNA on a confirmatory sample obtained immediately prior to the initiation of treatment for CMV disease or PET, as measured by the Roche CAP/CTM assay in a central laboratory. Detectable CMV viral DNA includes reporting of PCR results as detected but not quantifiable, or detected with a numeric value. The lower limit of quantification for viremia using this instrument is 137 IU/mL or approximately 150 copies/mL based on a conversion factor of 1.1 copies/IU as per the assay package insert. According to the clinical experts consulted for this CDR review and an overview of prevention of viral infections in HSCTs, there are no well-established viremia thresholds used to initiate PET for CMV infection; however, in Canadian clinical practice, most clinicians would initiate PET for patients whose viral loads reach ≥ 1,000 copies/mL.[10] Still, this threshold may vary depending on the patient's CMV infection risk factors (e.g., donor serostatus, GVHD, and immunosuppression). Patients at low risk of CMV infection would likely initiate PET at ≥ 1,000 copies/mL whereas patients at high risk may initiate PET at ≤ 1,000 copies/mL. Sensitivity analyses were performed at viral loads between 150 copies/mL and 300 copies/mL to demonstrate the robustness of the treatment effect at varying viral loads.

The treatment effect on the primary efficacy end point in Study P001 was evaluated within pre-specified subgroups of interest to this review (e.g., age, risk of CMV infection). Given that no interaction tests for the subgroup analyses were conducted, the interpretation of the results is limited.[54]

Patients in Study P001 received treatment up to week 14 post-transplant. However, the treatment effect associated with letermovir therapy was evaluated through both week 14 post-transplant and week 24 post-transplant, of which the primary end point was evaluated at the later time point (the end point at week 14 post-transplant was considered a

secondary end point). The clinical experts consulted for this review indicated that when patients are treated in a PET setting, the majority of patients do not reactivate. However, some patients may reactivate following treatment as not all patients are in the same risk group. Therefore, assessing the primary outcome at 24 weeks (10 weeks after the cessation of therapy) in Study P001 may be considered a more conservative approach.

The manufacturer undertook a post hoc analysis of CMV-related mortality defined as death due to any reason in patients who met the primary end point to provide additional information related to the all-cause mortality. However, according to FDA, the interpretation of the results is limited given that the definition of CMV-related mortality may be misleading because clinically significant CMV infection may or may not have caused mortality (this can be subjective).[55,56] In addition, even if there was no difference in CMV-related mortality between treatment arms, given the definition of CMV-related mortality, statistical significance in this end point could have been achieved based on the statistical significance in the difference in clinically significant CMV infection between the two groups.

In Study P001, no secondary end points were corrected for multiple statistical testing. Further, adjustments for inflated type I error were also not performed for any subgroups or sensitivity analyses. As a result, all analyses other than the primary analysis of the primary end point (clinically significant CMV infection through week 24 post-transplant) are subject to increased risk of making a type 1 error.

External Validity

Study P001 was multinational and included 19 patients from one site in Canada. The clinical experts consulted by CDR for this review highlighted that Study P001 appears to have recruited patients with characteristics similar to those of the overall CMV-seropositive recipients of an allogeneic HSCT in Canada. The experts noted that the population enrolled (68.0% of patients were between 36 and 64 years of age) may represent a slightly younger population than would be observed in Canadian clinical practice. However, the slight difference was not considered to be of concern. Furthermore, the experts noted that approximately 25% of patients received non-myeloablative conditioning regimen which is not typically used in Canada, and a reduced frequency of antithymocyte globulin use (approximately 38%) compared with what would be seen in Canadian clinical practice. The experts indicated that these differences are unlikely to affect the generalizability of the trial results to the Canadian population.

Patients in Study P001 could only receive treatment up to week 14 post-transplant. The clinical experts consulted for this CDR suggested that some clinicians may be interested in treating patients with certain CMV infection risk factors (e.g., donor serostatus, GVHD, and immunosuppression) for longer periods of time than those conducted in the trial to mitigate the potential for CMV infection long term. However, Study P001 does not provide any data to assess the safety and efficacy of letermovir beyond 14 weeks of treatment.

Using a PET treatment strategy, most patients in Canadian clinical practice would receive treatment for CMV infection at viral loads ≥ 1,000 copies/mL. When patients are treated on a prophylactic basis for CMV infection, the clinical experts indicated that the threshold for initiating treatment for CMV infection is likely to be lower than 1,000 copies/mL given the reduced tolerance for CMV replication. Therefore, the initiation of PET at viral thresholds ≤ 1,000 copies/mL in patients treated prophylactically with letermovir is likely reasonable. (Initiation at such thresholds was done in Study P001 where treatment was initiated when viral loads were detected but not quantifiable, or detected with a numeric value of

approximately 150 copies/mL.) However, because patients in the placebo group were initiated on PET at lower thresholds than would be seen in clinical practice, there is a lack of comparative evidence for letermovir versus a PET strategy that is based on an initiation of therapy at viral thresholds normally used in clinical practice (approximately 1,000 copies/mL, depending on patient risk factors).

Efficacy

The following table, Table 5, reports only those efficacy outcomes identified in the CDR protocol. See Appendix 3 for detailed efficacy data.

Clinically Significant Cytomegalovirus Infection

Week 24 Post-Transplant

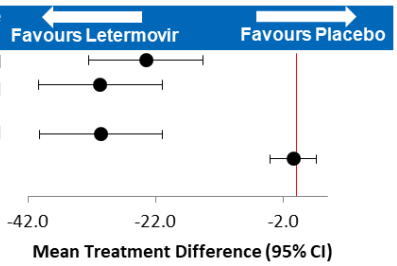
Compared with placebo, letermovir was associated with a statistically significant reduction in clinically significant CMV infection at week 24 post-transplant (the primary outcome), using the primary method for imputing data (non-completers and missing data are considered as having met the primary end point). The stratum-adjusted mean difference was −23.5% (95% CI, −32.5 to −14.6) $P < 0.0001$ in favour of letermovir. This end point was driven by two components based on observed data only: initiation of PET based on documented viremia and clinical condition of the patient and CMV end-organ disease (stratum-adjusted mean differences were −30.6% [95% CI, −40.2 to −21.0] $P < 0.0001$ and −0.4% [95% CI, −4.0 to 3.2] $P = 0.4056$, respectively). Details about the primary outcome in Study P001 are provided in Table 15. The results of sensitivity analyses of the primary outcome were consistent with the primary analysis of the primary end point (Table 15 and

Table 24). The sensitivity analyses results of the primary outcome were based only on observed data (no imputation of data), a PP population, and on patients with detectable CMV viral DNA on day 1.

The primary efficacy outcome was also analyzed in several pre-specified subgroups. Results were mostly consistent with the primary analysis with the exception of the donor human leukocyte antigen matched and related HSCT, the donor human leukocyte antigen-mismatched and unrelated HSCT, and the age category ≥ 65 years of age subgroups in which there were no apparent differences between treatment arms (stratum-adjusted mean differences were −12.1% [95% CI, −28.1 to 3.8], −7.4% [95% CI, −33.7 to 18.8] and −18.9% [95% CI, −41.7 to 3.9], respectively). Details about the subgroup analyses of the primary outcome in Study P001 are provided in Table 23.

Table 15: Clinically Significant Cytomegalovirus Infection Through Week 24 Post-Transplant (Full Analysis Set)

End Point	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value
Clinically Significant CMV infection[ab]	**122/325 (37.5)**	**103/170 (60.6)**	**−23.5 (-32.5, -14.6)**	**< 0.0001**
Clinically significant CMV infection by week 24[c]	57/260 (21.9)	71/138 (51.4)	−30.7 (-40.3, -21.0)	< 0.0001
Initiation of PET based on documented CMV viremia[c]	52/258 (20.2)	68/137 (49.6)	−30.6 (-40.2, -21.0)	< 0.0001
CMV end-organ disease[c]	5/254 (2.0)	3/123 (2.4)	−0.4 (-4.0, 3.2)	0.4056
Discontinued from study before week 24	56/325 (17.2)	27/170 (15.9)		
Missing outcome in week 24 visit window	9/325 (2.8)	5/170 (2.9)		



CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; *P* = probability; PET = pre-emptive therapy.

Note: Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the patient. Ninety-five per cent CIs and *P* value for the treatment differences in per cent response were calculated using stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided *P* value ≤ 0.0249 was used for declaring statistical significance. No adjustments for multiple statistical tests were made for any outcomes other than the primary efficacy end point.

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[b] The primary analysis included all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window.

[c] Sensitivity analysis of the primary end point based on observed data only, missing data for a particular end point was excluded from the analysis.

Source: P001 V01 CSR.[23]

Time to Clinically Significant CMV Infection Through Week 24 Post-Transplant

A Kaplan–Meier (KM) plot of the time to onset of clinically significant CMV infection through week 24 post-transplant is presented in Figure 3. The KM event rates in the letermovir and the placebo group were 6.8% and 41.3% through week 14 post-transplant compared with 18.9% and 44.3% through week 24 post-transplant, respectively. Figure 4 and Figure 5 present time to onset data for the individual components (initiation of PET based on documented viremia and CMV end-organ disease through week 24 post-transplant) of the end point (clinically significant CMV infection through week 24 post-transplant). The overall initiation of PET based on documented viremia KM event rates at week 24 post-transplant were 17.2% and 42.4% in the letermovir and placebo groups, respectively. The KM event rates of CMV end-organ disease (the other component of clinically significant CMV) were 1.8% and 2.1% in the letermovir and placebo groups, respectively.

Week 14 Post-Transplant

Clinically significant CMV infection was also evaluated through week 14 post-transplant (on treatment phase) in Study P001 as a secondary outcome using the primary method for imputing data (non-completers and missing data are considered failures having met the primary end point). The results were consistent with the results at week 24 post-transplant. The stratum-adjusted mean difference was −31.3% (95% CI, −39.9 to −22.6) $P < 0.0001$. This end point was driven by two components based on observed data only: initiation of PET based on documented viremia and clinical condition of the patient and CMV end-organ disease (stratum-adjusted mean differences were −35.3% [95% CI, −43.8 to −26.8] $P < 0.0001$ and −1.0% [95%CI, −3.5 to 1.5] $P = 0.2258$, respectively). Details about clinically significant CMV infection through week 14 post-transplant in Study P001 are provided in Table 16.

The results of sensitivity analyses (based only on observed data [no imputation of data] and a PP population) of clinically significant CMV infection through week 14 post-transplant were also consistent with the results at week 24 post-transplant (Table 16 and Table 24).

Initiation of PET

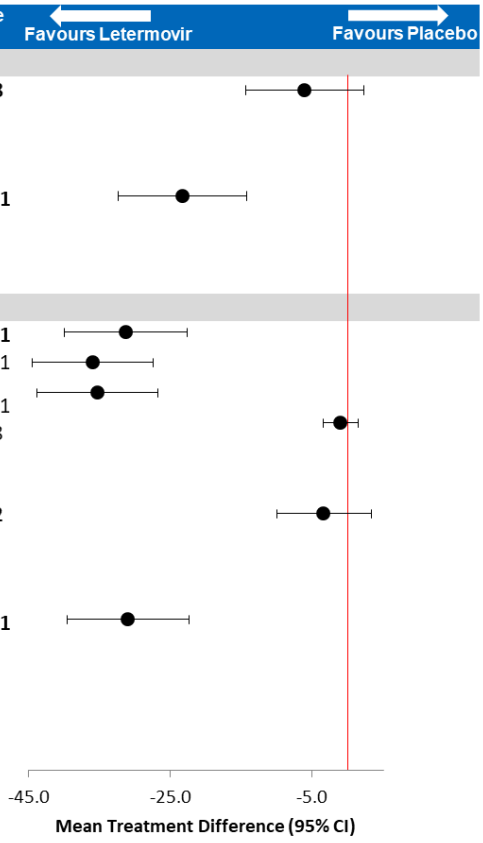
Initiation of PET was based on documented viremia and clinical condition of the patient; a component of the primary end point was also evaluated through both week 14 post-transplant and week 24 post-transplant as a secondary outcome, using the primary method for imputing data (non-completers and missing data are considered failures having met the primary end point). The stratum-adjusted mean differences were –31.0% (95% CI, –39.6 to –22.4) $P < 0.0001$ and –23.3% (95% CI, –32.3 to –14.3) $P < 0.0001$, respectively. Details about the initiation of PET based on documented viremia in Study P001 are provided in Table 16. The results of sensitivity analyses of PET initiation based on documented viremia through weeks 14 and 24 were also evaluated. The sensitivity analyses results of PET initiation were based only on observed data (no imputation of data), CMV DNA results from the local laboratory, a PP population, and PP-recommended viral load threshold for the initiation of PET. The stratum-adjusted MD of the sensitivity analyses through week 14 post-transplant and through week 24 post-transplant were similar (magnitude and direction). Details about the sensitivity analyses of PET initiation based on documented viremia in Study P001 are provided in Table 15, Table 16, and Table 25.

Morbidity (e.g., CMV Disease, End-Stage Organ Disease)

CMV end-organ disease (a component of the primary end point) was evaluated through both week 14 post-transplant and week 24 post-transplant as a secondary end point using the primary method for imputing data (non-completers and missing data are considered as having met the primary end point). The stratum-adjusted mean differences were –3.4% (95% CI, –10.0 to 3.3) $P < 0.1622$ and –6.1% (95% CI, –14.4 to 2.2) $P < 0.0748$, respectively. Details about CMV end-organ disease in P001 are provided in Table 16. The results of sensitivity analyses (based only on observed data [no imputation of data], a PP population) of CMV end-organ disease through weeks 14 and 24 were also evaluated. The stratum-adjusted MD of the sensitivity analyses through week 14 post-transplant, and through week 24 post-transplant, were similar (magnitude and direction). Details about the sensitivity analyses of CMV end-organ disease in P001 are provided in Table 16 and Table 25.

Table 16: Initiation of Pre-Emptive Therapy and Cytomegalovirus End-Organ Disease Through Week 24/14 Post-Transplant (Full Analysis Set)

End Point	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value
Week 24 Post-Transplant				
CMV End-Organ Disease[ab]	**76/325 (23.4)**	**50/170 (29.4)**	**−6.1 (-14.4, 2.2)**	**0.0748**
CMV end-organ disease	5/325 (1.5)	3/170 (1.8)		
Discontinued from study before week 24	61/325 (18.8)	38/170 (22.4)		
Missing outcome in week 24 visit window	10/325 (3.1)	9/170 (5.3)		
Initiation of PET[ab]	**119/325 (36.6)**	**101/170 (59.4)**	**−23.3 (-32.3, -14.3)**	**< 0.0001**
Initiation of PET for documented CMV viremia	52/325 (16)	68/170 (40)		
Discontinued from study before week 24	57/325 (17.5)	28/170 (16.5)		
Missing outcome in week 24 visit window	10/325 (3.1)	5/170 (2.9)		
Week 14 Post-Transplant				
Clinically Significant CMV Infection[ab]	**62/325 (19.1)**	**85/170 (50)**	**−31.3 (-39.9, -22.6)**	**< 0.0001**
Clinically significant CMV infection by week 14[c]	25/288 (8.7)	67/152 (44.1)	−36.0 (-44.5, -27.4)	< 0.0001
Initiation of PET based on documented CMV viremia[c]	24/288 (8.3)	65/151 (43.0)	−35.3 (-43.8, -26.8)	< 0.0001
CMV end-organ disease[c]	1/285 (0.4)	2/170 (1.4)	−1.0 (-3.5, 1.5)	0.2258
Discontinued from study before week 14	33/325 (10.2)	16/170 (9.4)		
Missing outcome in week 14 visit window	4/325 (1.2)	2/170 (1.2)		
CMV End-Organ Disease[ab]	**41/325 (12.6)**	**27/170 (15.9)**	**−3.4 (-10.0, 3.3)**	**0.1622**
CMV end-organ disease	1/325 (0.3)	2/170 (1.2)		
Discontinued from study before week 14	35/325 (10.8)	20/170 (11.8)		
Missing outcome in week 14 visit window	5/325 (1.5)	5/170 (2.9)		
Initiation of PET[ab]	**61/325 (18.8)**	**84/170 (49.4)**	**−31.0 (-39.6, -22.4)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	24/325 (7.4)	65/170 (38.2)		
Discontinued from study before week 14	33/325 (10.2)	17/170 (10)		
Missing outcome in week 14 visit window	4/325 (1.2)	2/170 (1.2)		



CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; *P* = probability; PET = pre-emptive therapy.

Note: Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the patient. Ninety-five per cent CIs and *P* value for the treatment differences in per cent response were calculated using stratum-adjusted Mantel–Haenszel method, with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided *P* value ≤ 0.0249 was used for declaring statistical significance. No adjustments for multiple statistical tests were made for any outcomes other than the primary efficacy end point.

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
[b] The primary analysis included all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through the week 24 post-transplant visit window.
[c] Sensitivity analysis of the secondary end point based on observed data only; missing data for a particular end point was excluded from the analysis.

Source: P001 V01 CSR.[23]

Mortality

Details about mortality (exploratory end points) through weeks 14, 24, and 48 post-transplant in Study P001 are provided in Table 17.

All-Cause Mortality

All-cause mortality was reported through weeks 14, 24, and 48 post-transplant with frequencies of 5.2%, 9.8%, and 18.8% in the letermovir arm compared with 7.1%, 15.9%,

and 23.5% in the placebo arm, respectively. All-cause mortality at week 48 post-transplant was also reported in patients without clinically significant CMV infection with frequency of 19.4% in the letermovir arm compared with 18.2% in the placebo arm, respectively.

A KM plot of the time to all-cause mortality through week 24 and week 48 post-transplant is presented in Figure 6. The KM event rates in the letermovir arm and the placebo arm were 10.2% and 15.9% at week 24 post-transplant and 20.9% and 25.5% at week 48 post-transplant, respectively.

All-Cause Mortality in Patients Meeting the Primary End Point

All-cause mortality in patients who met the primary end point was reported through weeks 14, 24, and 48 post-transplant with frequencies of 0.3%, 0.9%, and 2.8% in the letermovir arm compared with 1.8%, 8.2%, and 13.5% in the placebo arm, respectively. All-cause mortality at 48 weeks in patients with the primary end point at week 24 post-transplant was also reported with frequency of 15.8% in the letermovir arm compared with 31.0% in the placebo arm.

A KM plot of the time to all-cause mortality in patients who met the primary end point through week 24 and week 48 is presented post-transplant in Figure 7. The KM event rates in the letermovir arm and the placebo arm were 0.7% and 9.1% at week 24 post-transplant and 3.6% and 16.0% at week 48 post-transplant, respectively.

Non-Relapse Mortality

Death due to any reason other than the primary condition for which the transplant was performed was reported through weeks 14, 24, and 48 post-transplant with frequencies of 4.0%, 6.5% and, 12.0% in the letermovir arm compared with 5.3%, 10.6%, and 15.9% in the placebo arm, respectively.

A KM plot of the time to non-relapse mortality through week 24 and week 48 post-transplant is presented in Figure 8. The KM event rates in the letermovir arm and the placebo arm were 6.9% and 11.7% at week 24 post-transplant and 13.7% and 17.8% at week 48 post-transplant, respectively.

Graft-Versus-Host Disease (Acute and Chronic)

Details regarding the occurrence of GVHD (exploratory end points) through weeks 14, 24, and 48 post-transplant in Study P001 are provided in Table 17.

Any GVHD

All occurrences of GVHD were reported through weeks 14, 24, and 48 post-transplant with frequencies of 38.8%, 48.9%, and 58.5% in the letermovir arm compared with 41.8%, 54.7%, and 60.6% in the placebo arm, respectively.

Acute GVHD

Acute GVHD through weeks 14, 24, and 48 post-transplant was also reported with frequencies of 38.8%, 44.6%, and 48.6% in the letermovir arm compared with 41.2%, 48.8%, and 50.0% in the placebo arm, respectively.

Chronic GVHD

Chronic GVHD through weeks 14, 24, and 48 post-transplant was also reported with frequencies of 0.6%, 7.7%, and 21.8% in the letermovir arm compared with 0.6%, 10.0%, and 23.5% in the placebo arm, respectively.

Infections Other than CMV

Bacterial and/or fungal opportunistic infections were evaluated as exploratory end points and reported through weeks 14, 24, and 48 post-transplant with frequencies of 24.0%, 26.8%, and 34.5% in the letermovir arm compared with 21.8%, 25.3%, and 32.4% in the placebo arm, respectively. Details about bacterial and/or fungal opportunistic infections through weeks 14, 24, and 48 post-transplant in P001 are provided in Table 17.

Hospitalization and Re-Hospitalization

Details regarding the occurrence of re-hospitalization (exploratory end points) through weeks 14, 24, and 48 post-transplant in Study P001 are provided in Table 17.

All-Cause Re-Hospitalization

Re-hospitalizations for any reason following initial hospital discharge were reported through weeks 14, 24, and 48 post-transplant with frequencies of 36.3%, 48.6%, and 55.7% in the letermovir arm compared with 47.6%, 55.3%, and 60.6% in the placebo arm, respectively.

Re-Hospitalization for CMV Infection

Re-hospitalizations for CMV infection and CMV disease following initial hospital discharge were reported through weeks 14, 24, and 48 post-transplant with frequencies of 0.6%, 3.1%, and 3.1% in the letermovir arm compared with 7.1%, 7.6%, and 8.0% in the placebo arm, respectively.

Table 17: Other Efficacy Outcomes Through Week 24 and Week 14 Post-Transplant (Full Analysis Set)

Outcome	Study P001	
	Letermovir N = 325	Placebo N = 170
Week 14 Post-Transplant, n (%)		
All-cause mortality	17 (5.2)	12 (7.1)
Non-relapse mortality	13 (4.0)	9 (5.3)
All-cause mortality in patients with clinically significant CMV at week 14 post-transplant	1 (0.3)	3 (1.8)
Bacterial and/or fungal opportunistic infection	78 (24.0)	37 (21.8)
Any GVHD	126 (38.8)	71 (41.8)
Acute GVHD:	126 (38.8)	70 (41.2)
Grade I	56 (17.2)	30 (17.6)
Grade II	48 (14. 8)	29 (17.1)
Grade III	16 (4.9)	7 (4.1)
Grade IV	6 (1.8)	4 (2.4)
≥ Grade II	70 (21.5)	40 (23.5)
Chronic GVHD	2 (0.6)	1 (0.6)
All-cause re-hospitalization	118 (36.3)	81 (47.6)

Outcome	Study P001	
	Letermovir N = 325	Placebo N = 170
Re-hospitalization for CMV infection/disease	2 (0.6)	12 (7.1)
Documented CMV viremia	103 (31.7)	118 (69.4)
Week 24 Post-Transplant, n (%)		
All-cause mortality	32 (9.8)	27 (15.9)
Non-relapse mortality	21 (6.5)	18 (10.6)
All-cause mortality in patients with clinically significant CMV at week 24 post-transplant	3 (0.9)	14 (8.2)
Bacterial and/or fungal opportunistic infection	87 (26.8)	43 (25.3)
Any GVHD	159 (48.9)	93 (54.7)
Acute GVHD:	145 (44.6)	83 (48.8)
Grade I	64 (19.7)	36 (21.2)
Grade II	56 (17.2)	32 (18.8)
Grade III	18 (5.5)	9 (5.3)
Grade IV	7 (2.2)	6 (3.5)
≥ Grade II	81 (24.9)	47 (27.6)
Chronic GVHD	25 (7.7)	17 (10.0)
All-cause re-hospitalization	158 (48.6)	94 (55.3)
Re-hospitalization for CMV infection/disease	10 (3.1)	13 (7.6)
Documented CMV viremia	186 (57.2)	124 (72.9)
Week 48 Post-Transplant, (%)		
All-cause mortality	61 (18.8)	40 (23.5)
Patients without clinically significant CMV infection, n/N (%)	52/268 (19.4)	18/99 (18.2)
Non-relapse mortality	39 (12.0)	27 (15.9)
All-cause mortality in patients with clinically significant CMV at week 24 post-transplant, n/N (%)	9/57 (15.8)	22/71 (31.0)
All-cause mortality in patients with clinically significant CMV at week 48 post-transplant	9 (2.8)	23 (13.5)
Bacterial and/or fungal opportunistic infection	112 (34.5)	55 (32.4)
Any GVHD	190 (58.5)	103 (60.6)
Acute GVHD:[a]	158 (48.6)	85 (50.0)
Grade I	73 (22.5)	37 (21.8)
Grade II	57 (17.5)	30 (17.6)
Grade III	20 (6.2)	10 (5.9)
Grade IV	8 (2.5)	8 (4.7)
≥ Grade II	85 (26.2)	48 (28.2)
Chronic GVHD[b]	71 (21.8)	40 (23.5)
All-cause re-hospitalization	181 (55.7)	103 (60.6)
Re-hospitalization for CMV infection/disease	10 (3.1)	15 (8.8)
Documented CMV viremia	NR	NR
CMV end-organ disease	8 (2.5)	6 (3.5)

CMV = cytomegalovirus; CSR = Clinical Study Report; GVHD = graft-versus-host disease; N = total number in the sample under study; n = number in a subgroup of the sample under study; NR = not reported.

Note: Each patient counted only one time as acute GVHD and/or only one time as chronic GVHD.

[a] Patients were considered to have acute GVHD if the date of onset was prior to 100 days post-transplant or if a grade was reported after 100 days post-transplant.

[b] Patients were considered to have chronic GVHD if the onset date was after 100 days post-transplant or if no grade was reported prior to 100 days post-transplant.

Source: P001 V01 CSR,[23] P001 V02 CSR.[24]

Antiviral Resistance (Genotypic Variance)

Resistance to letermovir was evaluated as an exploratory end point in Study P001. Among the 22 patients in the FAS who received letermovir and had next-generation DNA sequencing testing for GVs and resistance were 10 non-previously described or characterized UL56 GVs, two common non-characterized GVs, and one previously characterized letermovir-resistant GV. For UL89, there were five common non-characterized GVs and five non-previously described or characterized GVs.

Table 18: Genotypic Variants of UL56 and UL89 (Full Analysis Set)

Genotypic Variant	Study P001	
	Letermovir N = 325	Placebo N = 170
UL56, n/N (%)		
Patients with genotypic variant detected	20/22 (91.0)	36/41 (88.0)
GV characterized for Letermovir resistance		
Mutation V236M	1/22 (4.5)	0
Non-characterized or described GV	10/22 (45.5)	NR
Common non-characterized GV	2/22 (9.1)	NR
UL89, n/N (%)		
Patients with genotypic variant detected	12/19 (63.0)	25/38 (66.0)
GV characterized for Letermovir resistance	NR	NR
Non-characterized or described GV	5/22 (22.7)	NR
Common non-characterized GV	5/22 (22.7)	NR

CSR = Clinical Study Report; GV = genotypic variant; N = total number in the sample under study; n = number in a subgroup of the sample under study; NR = not reported.

Note: Differences detected at a frequency of ≥ 5% of the total sequence data at a given position indicate the presence of a CMV genotypic variant.

Source: P001 V01 CSR.[23]

Quality of Life

EuroQol 5-Dimensions 3-Level Questionnaire

Study P001 evaluated health-related quality of life using the EQ-5D-3L questionnaire through weeks 14, 24, and 48 post-transplant. In general, EQ-5D index scores at baseline were similar across both treatment arms and ranged between 0.639 and 0.669. Through week 48 post-transplant, patients in the letermovir arm had index scores that ranged between 0.751 and 0.786 compared with 0.720 and 0.768 in the placebo arm. Similarly, the EuroQ0L Visual Analogue Scale (EQ VAS) scores at baseline were similar across both treatment arms and ranged between 62.3 and 62.9. Through week 48 post-transplant, patients in the letermovir arm had EQ VAS scores that ranged between 7.3 and 15.7 compared with 5.8 and 13.1 in the placebo arm. Details on the EQ-5D-3L are provided in Table 19.

Table 19: Summary of EuroQol 5-Dimensions 3-Level (Full Analysis Set)

EQ-5D	Study P001	
	Letermovir N = 325	Placebo N = 170
EQ-5D Index Score		
Baseline, n (%)	243	135
Baseline, mean (SD)	0.639 (0.3438)	0.669 (0.2854)
Week 14 Post-Transplant		
Number of patients, n (%)	193	98
Mean (SD)	0.753 (0.2867)	0.720 (0.2836)
Mean change from baseline (SD)	0.107 (0.3726)	0.025 (0.3540)
MD vs. placebo (95% CI)	NR	
Week 24 Post-Transplant		
Number of patients, n (%)	149	72
Mean (SD)	0.751 (0.2859)	0.758 (0.2701)
Mean change from baseline (SD)	0.108 (0.3822)	0.040 (0.3738)
MD vs. placebo (95% CI)	NR	
Week 48 Post-Transplant		
Number of patients, n (%)	142	74
Mean (SD)	0.786 (0.2503)	0.768 (0.2856)
Mean change from baseline (SD)	0.164 (0.3534)	0.084 (0.3840)
MD vs. placebo (95% CI)	NR	
EQ-5D VAS		
Baseline, n (%)	243	135
Baseline, mean (SD)	62.9 (20.54)	62.3 (19.45)
Week 14 Post-Transplant		
Number of patients, n (%)	193	98
Mean (SD)	70.5 (18.20)	67.8 (18.91)
Mean change from baseline (SD)	7.3 (20.45)	5.8 (21.66)
MD vs. placebo (95% CI)	NR	
Week 24 Post-Transplant		
Number of patients, n (%)	149	72
Mean (SD)	70.2 (19.63)	73.3 (15.24)
Mean change from baseline (SD)	8.1 (23.93)	12.2 (20.86)
MD vs. placebo (95% CI)	NR	
Week 48 Post-Transplant		
Number of patients, n (%)	142	74
Mean (SD)	77.6 (16.29)	74.6 (19.04)
Mean change from baseline (SD)	15.7 (21.89)	13.1 (23.30)
MD vs. placebo (95% CI)	NR	

CI = confidence interval; CSR = Clinical Study Report; EQ-5D = EuroQol 5-Dimensions; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; NR = not reported; SD = standard deviation; VAS = Visual Analogue Scale.

Source P001 V02 CSR.[24]

Functional Assessment of Cancer Therapy – Bone Marrow Transplant Questionnaire

Study P001 evaluated quality of life using the FACT-BMT questionnaire through weeks 14, 24, and 48 post-transplant. In general, FACT-BMT total scores at baseline were similar across both treatment arms and ranged between 99.0 and 99.2. Patients treated with letermovir typically had numerically higher total scores compared with placebo. Details on the FACT-BMT are provided in Table 20.

Table 20: Summary of Functional Assessment of Cancer Therapy – Bone Marrow Transplant (Full Analysis Set)

FACT-BMT	Study P001	
	Letermovir N = 325	Placebo N = 170
Total Score		
Baseline, n (%)	258	138
Baseline, mean (SD)	99.0 (20.30)	99.2 (18.28)
Week 14 Post-Transplant		
Number of patients, n (%)	212	102
Mean (SD)	103.8 (20.08)	100.0 (22.08)
Mean change from baseline (SD)	4.6 (19.09)	−0.1 (20.10)
MD vs. placebo (95% CI)	NR	
Week 24 Post-Transplant		
Number of patients, n (%)	163	77
Mean (SD)	104.6 (22.61)	103.4 (23.04)
Mean change from baseline (SD)	6.4 (17.73)	4.2 (20.69)
MD vs. placebo (95% CI)	NR	
Week 48 Post-Transplant		
Number of patients, n (%)	156	80
Mean (SD)	108.1 (21.97)	103.5 (23.99)
Mean change from baseline (SD)	10.0 (18.36)	5.8 (25.42)
MD vs. placebo (95% CI)	NR	

CSR = Clinical Study Report; FACT-BMT = Functional Assessment of Cancer Therapy – Bone Marrow Transplant; CI = confidence interval; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; NR = not reported; SD = standard deviation.

Source: P001 V02 CSR.[24]

Harms

The following table, Table 5, reports only those harms identified in the review protocol. See Appendix 3 for detailed harms data.

Adverse Events

Overall, 97.9% and 100%, 98.1% and 100%, and 98.4% and 100% of patients experienced AEs in the letermovir and placebo arms through weeks 14, 24, and 48 post-transplant, respectively. Overall, the frequencies of AEs were relatively similar across treatment arms. The most common AEs through week 48 post-transplant were edema peripheral (16.1% and 12.0%), pyrexia (24.7% and 27.6%), rash (24.1% and 26.6%), headache (16.1% and 12.5%), and cough (16.6% and 14.1%) in the letermovir and placebo arms, respectively.

Serious Adverse Events

Similar frequencies of serious AEs were reported in the letermovir arm compared with the placebo arm (44.2% and 46.9%, 51.7% and 56.8%, and 54.2% and 59.9% through weeks 14, 24, and 48 post-transplant, respectively). The most common serious AEs through week 48 post-transplant were pneumonia (4.0% and 3.1%), septic shock (1.3% and 3.6%), acute myeloid leukemia recurrent (6.2% and 8.9%), and acute kidney injury (1.9% and 4.7%) in the letermovir and placebo arms, respectively.

Withdrawals Due to Adverse Events

Withdrawals due to AEs were only reported through week 24 post-transplant and were similar between treatment arms (1.5% and 1.6% in the placebo arm and letermovir arm, respectively). Overall, a greater frequency of treatment discontinuation was reported in the placebo arm compared with the letermovir arm (51.0% and 19.3%, respectively). This may be primarily due to a higher proportion of patients discontinuing due to CMV infection (6.2% and 39.1% in the letermovir arm and placebo arm, respectively).

Mortality

A total of 38 and 17, 61 and 38, and 81 and 47 deaths occurred in the letermovir arm and placebo arm at weeks 14, 24, and 48 post-transplant, respectively. The most frequently reported reasons for death through week 14 post-transplant (letermovir versus placebo) were GVHD (1.3% vs. 1.6%), recurrent acute myeloid leukemia (1.9% vs. 1.6%), septic shock (0.8% vs. 1.6%), and sepsis (0.8% vs. 0.5%). However, none of the deaths was considered to be related to study treatment by the investigators.

Notable Harms

The occurrence of notable harms — specifically, cardiac disorders and gastrointestinal disorders — was approximately equivalent in both treatment arms through weeks 14, 24, and 48 post-transplant, with the exception of cardiac disorders through week 14 post-transplant. A total of 47 patients (12.6%) and 12 patients (6.3%) experienced cardiac disorders in the letermovir arm and placebo arm, respectively, through week 14 post-transplant. The most common reasons for cardiac disorders in the letermovir arm and placebo arm were atrial fibrillation (3.5% and 1.0%), sinus tachycardia (1.1% and 1.6%), and tachycardia (4.0% and 2.1%), respectively. A total of 53 patients (14.2%) and 20 patients (10.4%) experienced cardiac disorders in the letermovir arm and placebo arm, respectively, through week 48 post-transplant. The most common cardiac disorders through week 48 post-transplant in the letermovir arm and placebo arm were atrial fibrillation (3.5% and 1.0%), sinus tachycardia (1.1% and 2.6%), and tachycardia (4.8% and 2.6%), respectively.

A total of 279 patients (74.8%) and 141 patients (73.4%) in the letermovir arm and placebo arm, respectively, experienced gastrointestinal disorders through week 48 post-transplant. The most common gastrointestinal disorders through week 48 post-transplant in the letermovir arm and placebo arm were abdominal pain (13.1% and 9.9%), diarrhea (29.5% and 28.6%), nausea (28.7% and 27.6%), and vomiting (21.4% and 18.2%), respectively.

Table 21: Harms (All Patients as Treated)

Harms, n (%)	Study P001					
	Week 14		Week 24		Week 48	
	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192
AEs						
Patients with > 0 AEs	365 (97.9)	192 (100)	366 (98.1)	192 (100)	367 (98.4)	192 (100)
Most Common AEs[a]						
Febrile neutropenia	31 (8.3)	18 (9.4)	33 (8.8)	21 (10.9)	35 (9.4)	21 (10.9)
Fatigue	50 (13.4)	21 (10.9)	52 (13.9)	25 (13.0)	55 (14.7)	26 (13.5)
Mucosal inflammation	46 (12.3)	24 (12.5)	47 (12.6)	24 (12.5)	47 (12.6)	24 (12.5)
Edema peripheral	54 (14.5)	18 (9.4)	57 (15.3)	22 (11.5)	60 (16.1)	23 (12.0)
Pyrexia	77 (20.6)	43 (22.4)	86 (23.1)	50 (26.0)	92 (24.7)	53 (27.6)
Blood creatinine increased	36 (9.7)	13 (6.8)	38 (10.2)	15 (7.8)	40 (10.7)	15 (7.8)
Decreased appetite	38 (10.2)	22 (11.5)	40 (10.7)	25 (13.0)	44 (11.8)	28 (14.6)
Back pain	23 (6.2)	14 (7.3)	24 (6.4)	20 (10.4)	24 (6.4)	20 (10.4)
Headache	52 (13.9)	18 (9.4)	57 (15.3)	23 (12.0)	60 (16.1)	24 (12.5)
Acute kidney injury	36 (9.7)	25 (13.0)	41 (11.0)	29 (15.1)	41 (11.0)	29 (15.1)
Cough	53 (14.2)	20 (10.4)	62 (16.6)	28 (14.6)	62 (16.6)	27 (14.1)
Rash	76 (20.4)	41 (21.4)	86 (23.1)	48 (25.0)	90 (24.1)	51 (26.6)
Hypertension	31 (8.3)	21 (10.9)	32 (8.6)	23 (12.0)	34 (9.1)	24 (12.5)
SAEs						
Patients with > 0 SAEs	165 (44.2)	90 (46.9)	193 (51.7)	109 (56.8)	202 (54.2)	115 (59.9)
Most Common SAEs[b]						
Diarrhea	2 (0.5)	5 (2.6)	3 (0.8)	5 (2.6)	3 (0.8)	5 (2.6)
Multiple organ dysfunction syndrome	0	2 (1.0)	1 (0.3)	4 (2.1)	2 (0.5)	4 (2.1)
Pyrexia	7 (1.9)	4 (2.1)	9 (2.4)	4 (2.1)	10 (2.7)	4 (2.1)
Pneumonia	8 (2.1)	3 (1.6)	14 (3.8)	4 (2.1)	15 (4.0)	6 (3.1)
Sepsis	5 (1.3)	2 (1.0)	7 (1.9)	3 (1.6)	8 (2.1)	4 (2.1)
Septic shock	4 (1.1)	5 (2.6)	5 (1.3)	6 (3.1)	5 (1.3)	7 (3.6)
Acute myeloid leukemia	4 (1.1)	2 (1.0)	5 (1.3)	4 (2.1)	7 (1.9)	4 (2.1)
Acute myeloid leukemia recurrent	11 (2.9)	7 (3.6)	20 (5.4)	14 (7.3)	23 (6.2)	17 (8.9)
Acute kidney injury	5 (1.3)	9 (4.7)	7 (1.9)	9 (4.7)	7 (1.9)	9 (4.7)
WDAEs						
WDAEs	NR	NR	6 (1.6)	3 (1.5)	NR	NR
Treatment WDAEs						
Patients with > 0 WDAEs	72 (19.3)	98 (51.0)	72 (19.3)	98 (51.0)	73 (19.6)	99 (51.6)
Most Common Reasons[c]						
Nausea	6 (1.6)	2 (1.0)	NA	NA	NA	NA
Venoocclusive liver disease	2 (0.5)	2 (1.0)	NA	NA	NA	NA
Graft versus host disease	3 (0.8)	2 (1.0)	NA	NA	NA	NA
Cytomegalovirus infection	23 (6.2)	75 (39.1)	NA	NA	NA	NA
Septic shock	1 (0.3)	2 (1.0)	NA	NA	NA	NA
Acute myeloid leukemia recurrent	4 (1.1)	1 (0.5)	NA	NA	NA	NA

Harms, n (%)	Study P001					
	Week 14		Week 24		Week 48	
	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192	Letermovir N = 373	Placebo N = 192
Deaths						
Number of deaths	38 (10.2)	17 (8.9)	61 (16.4)	38 (19.8)	81 (21.7)	47 (24.5)
Notable Harms[b]						
Cardiac Disorders	**47 (12.6)**	**12 (6.3)**	**51 (13.7)**	**19 (9.9)**	**53 (14.2)**	**20 (10.4)**
Atrial fibrillation	13 (3.5)	2 (1.0)	13 (3.5)	2 (1.0)	13 (3.5)	2 (1.0)
Sinus tachycardia	4 (1.1)	3 (1.6)	4 (1.1)	5 (2.6)	4 (1.1)	5 (2.6)
Tachycardia	15 (4.0)	4 (2.1)	16 (4.3)	5 (2.6)	18 (4.8)	5 (2.6)
Gastrointestinal Disorders	**261 (70.0)**	**129 (67.2)**	**272 (72.9)**	**137 (71.4)**	**279 (74.8)**	**141 (73.4)**
Abdominal distension	4 (1.1)	3 (1.6)	4 (1.1)	4 (2.1)	4 (1.1)	5 (2.6)
Abdominal pain	44 (11.8)	18 (9.4)	48 (12.9)	19 (9.9)	49 (13.1)	19 (9.9)
Abdominal pain upper	15 (4.0)	16 (8.3)	19 (5.1)	16 (8.3)	23 (6.2)	17 (8.9)
Constipation	27 (7.2)	20 (10.4)	30 (8.0)	22 (11.5)	31 (8.3)	22 (11.5)
Diarrhea	97 (26.0)	47 (24.5)	105 (28.2)	52 (27.1)	110 (29.5)	55 (28.6)
Dry mouth	20 (5.4)	6 (3.1)	21 (5.6)	11 (5.7)	21 (5.6)	11 (5.7)
Flatulence	4 (1.1)	4 (2.1)	5 (1.3)	4 (2.1)	5 (1.3)	4 (2.1)
Dyspepsia	20 (5.4)	7 (3.6)	5 (1.3)	10 (5.2)	21 (5.6)	7 (3.6)
Gastroesophageal reflux disease	4 (1.1)	9 (4.7)	20 (5.4)	7 (3.6)	6 (1.6)	11 (5.7)
Hematochezia	4 (1.1)	2 (1.0)	5 (1.3)	10 (5.2)	4 (1.1)	4 (2.1)
Hemorrhoids	18 (4.8)	4 (2.1)	19 (5.1)	5 (2.6)	18 (4.8)	6 (3.1)
Lip dry	3 (0.8)	3 (1.6)	4 (1.1)	4 (2.1)	5 (1.3)	5 (2.6)
Nausea	9 (26.5)	45 (23.4)	102 (27.3)	50 (26.0)	107 (28.7)	53 (27.6)
Esophagitis	3 (0.8)	3 (1.6)	4 (1.1)	3 (1.6)	4 (1.1)	4 (2.1)
Stomatitis	23 (6.2)	9 (4.7)	23 (6.2)	13 (6.8)	24 (6.4)	14 (7.3)
Vomiting	69 (18.5)	26 (13.5)	74 (19.8)	32 (16.7)	80 (21.4)	35 (18.2)

AE = adverse event; CSR = Clinical Study Report; N = total number in the sample under study; n = number in a subgroup of the sample under study; NA = not applicable; NR = not reported; SAE = serious adverse event; WDAE = withdrawals due to adverse event.

[a] Frequency ≥ 10%.

[b] Frequency ≥ 2%.

[c] Frequency ≥ 1%.

Source: P001 V01 CSR,[23] P001 V02 CSR.[24]

Discussion

Summary of Available Evidence

One trial met the inclusion criteria of the CDR systematic review. Study P001 (N = 570) was a double-blind, placebo-controlled, multi-centre, multinational, phase III superiority randomized controlled trial and recruited patients from North America (including Canada). The study objective was to evaluate the efficacy and safety of letermovir as a preventive strategy for CMV infection in adults who are CMV-seropositive recipients of an allogeneic HSCT 24 weeks post-transplant. Patients were randomized to a 2:1 ratio of letermovir 480 mg administered either through IV infusion or orally (tablet) once daily (240 mg when co-administered with cyclosporine) or matching placebo. The primary efficacy end point was the incidence of clinically significant CMV infection through week 24 post-transplant, defined as the occurrence of either CMV end-organ disease or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the patient. Secondary outcomes included clinically significant CMV infection through week 14 post-transplant, initiation of PET as well as time to initiation of PET, and CMV end-organ disease and time to onset of CMV end-organ disease. Exploratory end points included mortality, opportunistic bacterial and/or fungal infections, GVHD, re-hospitalization, quality of life, and GV and antiviral resistance.

Limitations associated with the trial include no adjustments for multiple statistical testing other than the primary analysis of the primary efficacy end point, uncertainty with durability of the treatment effect and patient outcomes beyond 48 weeks post-transplant, and lack of comparative evidence in a true PET setting (initiation of PET at viral loads ≥ 1,000 copies/mL).

Interpretation of Results

Efficacy

Compared with placebo, letermovir was associated with a statistically significant reduction in the prevention of clinically significant CMV infection through week 24 post-transplant (the primary outcome) using the primary method for imputing data (non-completers and missing data are considered as having met the primary end point). Sensitivity analyses of the primary end point using observed data only (no imputation) and the PP population were also consistent with the primary analysis. The results at week 14 post-transplant (the maximum duration of letermovir treatment) and associated sensitivity analyses were also all consistent with the primary analysis. The robustness of the treatment effect was also noted by FDA.[55,56]

According to the clinical experts consulted for this CDR and an overview of prevention of viral infections in HSCTs, there are no well-established viremia thresholds used to initiate PET for CMV infection. However, in clinical practice, most clinicians would initiate PET for patients whose viral loads reach ≥ 1,000 copies/mL.[10] Still, this threshold may vary depending on the patient's CMV infection risk factors (e.g., donor serostatus, GVHD, and immunosuppression). Patients at low risk of CMV infection would likely initiate PET at ≥ 1,000 copies/mL whereas patients at high risk may initiate PET at ≤ 1,000 copies/mL. Sensitivity analyses were performed at viral loads between 150 copies/mL and 300 copies/mL to demonstrate the robustness of the treatment effect at varying viral loads.

Using a PET treatment strategy, most patients in clinical practice would receive treatment for CMV infection at viral loads ≥ 1,000 copies/mL. The clinical experts indicated that when patients are treated on a prophylactic basis for CMV infection, the threshold for initiating treatment for CMV infection is likely to be lower than 1,000 copies/mL given the reduced tolerance for CMV replication. Therefore, the initiation of PET at viral thresholds ≤ 1,000 copies/mL in patients treated prophylactically with letermovir is likely reasonable. (This was done in Study P001 where treatment was initiated when viral loads were detected but not quantifiable or detected with a numeric value of approximately 150 copies/mL.) However, because patients in the placebo arm were initiated on PET at lower thresholds than normally seen in clinical practice, there is a lack of comparative evidence for letermovir versus a PET strategy that is based on an initiation of therapy at viral thresholds that are usually used in clinical practice (approximately 1,000 copies/mL depending on patient risk factors). Analyses provided in Table 22 suggest that fewer patients with viral loads > 1,000 copies/mL met the primary end point in the letermovir group compared with the placebo group (5.9% compared with 21.2%), suggesting continued benefit despite higher viral thresholds. However, these same results may also suggest a reduced treatment effect in patients with higher viral loads.

The primary end point of clinically significant CMV infection includes multiple end points that are important to consider about CMV infection (i.e., the initiation of PET and CMV end-organ disease). Overall, the results are primarily driven by the reduction in the initiation of PET, whereas the event rates for CMV end-organ disease were sparse. Therefore, treatment with letermovir not only prevents clinically significant CMV infection compared with placebo, but should also result in fewer treatments with antiviral agents such as ganciclovir, which are typically associated with marrow toxicities.[14-16] These benefits were also noted by FDA.[55,56]

According to the same clinical experts, access to HSCT sites is limited and may require patients to temporarily travel to centres for treatment. In addition, patients are typically monitored for 100 days post-transplant for any signs of CMV infection, after which the patients would leave HSCT sites.[10] The same patients who require travel are also likely to have issues with access to monitoring post-transplant, thereby making PET difficult. The experts highlighted that the frequency of CMV monitoring post-transplant also depends on patient risk factors for CMV infection (e.g., donor serostatus, GVHD, immunosuppression) in addition to the patients' geographical location (access to monitoring for PET). Therefore, prophylactic treatment may be ideal in certain patients with limited access to CMV management.

Although CMV viral load is considered a surrogate marker, overall, there appears to be a correlation between viral load and negative outcomes, including the development of CMV disease, bacterial or fungal infections, and mortality. Some studies have generally reported that higher viral loads or CMV viremia at PET initiation (> 500 copies/mL) were indicative of the development of CMV disease[57,58] and late CMV disease,[59] and an increase in overall mortality and non-relapse mortality.[60] An increased risk in the development of invasive fungal diseases was also observed with infection of CMV post-allogeneic HSCT.[61] One study suggested that lower CMV viral loads have also been observed to be associated with shorter viremia episodes, a decreased risk for viremia lasting longer than 30 days, and shorter duration of treatment.[62] One important consideration that the authors noted was the fact that some of the CMV viremia that were treated at the lower viral loads may have resolved spontaneously, thus exposing patients to potentially unwanted AEs associated with PET. One study did not support the correlation between high viral load and the

development of CMV disease.[63] Overall, there is no consensus between the aforementioned identified studies regarding the exact viral load that determines the increased risk of progression from CMV viremia to CMV disease. However, this is likely due to the differences between viral load thresholds and the different time points examined in the individual studies.

Time to onset of clinically significant CMV infection through week 24 post-transplant was also evaluated as a secondary outcome using KM methods. An increase in the KM rate of events can be observed between weeks 14 and 24 in the letermovir arm only. Therefore, the time to event end points evaluated in Study P001 may suggest a potential increase in clinically significant CMV infection when patients are no longer treated with letermovir, which implies uncertainty in the durability of the treatment effect. A similar observation was also highlighted by FDA in which they suggest the potential benefit of longer prophylactic treatment in a subset of patients.[55,56] Health Canada also noted the increase in event rates between week 14 and week 24 post-transplant, and suggested possible reasons for failures beyond week 14 post-transplant, including onset of GVHD, concomitant steroid use after randomization, and high risk for CMV infection at baseline.[25]

The clinical experts consulted for this CDR suggested that for patients with ongoing CMV infection risk factors (e.g., donor serostatus, GVHD, and immunosuppression), there may be interest from clinicians to treat patients for longer periods of time than those conducted in the trial, to mitigate the potential for CMV infection long term. However, Study P001 does not provide any data to assess the safety and efficacy of letermovir beyond 14 weeks of treatment.

Mortality was also evaluated as an exploratory end point in Study P001. Overall, the frequency of all-cause mortality, non-relapse related mortality and CMV-related mortality was lower in the letermovir group compared with placebo group through weeks 14, 24, and 48 post-transplant. In general, deaths that occurred beyond 48 weeks were not followed up and were therefore not included in the mortality analyses. Subsequent to a request by FDA, the manufacturer submitted a re-analysis of the all-cause mortality end point, including deaths that occurred following week 48 post-transplant. Overall, FDA reports that the re-analysis suggests a more modest difference between treatment arms (76 deaths in the letermovir arm and 46 deaths in the placebo arm) when compared with the original analysis (61 deaths in the letermovir arm and 40 deaths in the placebo arm).

There were also issues with the interpretation of CMV-related death defined as death from any cause in patients who met the primary end point. Even if there was no difference in CMV-related mortality between the letermovir arm and placebo arm at the end point, statistical significance could have been driven due to the statistically significant difference in clinically significant CMV infection between the two treatment arms. These limitations associated with the mortality outcomes evaluated in Study P001 were also highlighted by FDA.[55,56]

Bacterial and/or fungal opportunistic infections, GVHD (acute or chronic), and re-hospitalization (all-cause or CMV-related) were also considered exploratory and were not adjusted for multiple statistical testing; therefore, no statistical interpretation should be made. Overall the frequency of bacterial and/or fungal opportunistic infections was similar between the two treatment arms, whereas the frequency of GVHD (acute or chronic) and re-hospitalization (all-cause or CMV-related) were lower in the letermovir arm compared with placebo arm through weeks 14, 24, and 48 post-transplant.

Study P001 also evaluated quality of life using the EQ-5D and FACT-BMT questionnaires. Given that these end points were considered exploratory and were not adjusted for multiple statistical testing, no statistical interpretation should be made. Therefore, the clinical importance of these changes remains unclear.

GVs and resistance associated with letermovir was also assessed in Study P001. Only one previously characterized letermovir-resistant GV was identified for UL56. All non-characterized GVs are to undergo phenotypic analysis to determine if the substitution has an impact on susceptibility to letermovir. At the time of this report, however, the phenotypic analyses were not provided.

Harms

Overall, a similar proportion of patients in the letermovir arm experienced AEs and serious AEs compared with the placebo group through weeks 14, 24, and 48 post-transplant. A greater frequency of treatment withdrawal due to AEs was reported in the placebo arm compared with the letermovir arm, which may be attributed to a higher proportion of patients discontinuing due to CMV infection.

The occurrence of notable harms — specifically, cardiac disorders and gastrointestinal disorders — was approximately equivalent in both treatment arms through weeks 14, 24, and 48 post-transplant, with the exception of cardiac disorders through week 14 post-transplant. Overall, more patients experienced cardiac disorders through week 14 post-transplant in the letermovir arm compared with the placebo arm. The most common reasons for cardiac disorders were atrial fibrillation, sinus tachycardia, and tachycardia. However, the differences between the two arms diminished through week 24 and week 48 post-transplant. The most common gastrointestinal disorders through week 48 post-transplant were abdominal pain, diarrhea, nausea, and vomiting, respectively. Overall, similar observations were also noted by FDA, in which they suggest that letermovir appears to have an acceptable AE profile and that the cardiac disorders observed in Study P001 were considered to be unrelated to the study drug (as per the investigators), and that many of the events occurred in patients with pre-existing medical conditions.

In general, there were more deaths in the placebo group through week 24 and week 48 post-transplant compared with the letermovir arm. In contrast, there were more deaths in the letermovir arm through week 14 post-transplant compared with the placebo arm. The most frequently reported reasons for death through week 14 post-transplant were GVHD, recurrent acute myeloid leukemia, septic shock, and sepsis. However, none of the deaths was considered to be related to study treatment by the investigators.

Prior to the availability of letermovir, prophylaxis with ganciclovir has been suggested as the most effective treatment for CMV disease; however, it may have limited use due to bone marrow toxicity.[14-16] High doses of other antivirals such as acyclovir and valacyclovir were reported to be less myelosuppressive than ganciclovir, although these agents also demonstrated inferior efficacy when compared with ganciclovir.[16-20] Given that both foscarnet and cidofovir can lead to severe myelotoxicity and nephrotoxicity, they are not the preferred agents for the management of CMV. Treatment with letermovir not only prevents clinically significant CMV infection compared with placebo, but should also result in fewer treatments with other more toxic antiviral agents such as ganciclovir. These benefits were also noted by FDA.[55,56]

Potential Place in Therapy[2]

CMV is one of the most common infections post-stem cell transplantation with both direct consequences (i.e., CMV disease) and indirect effects (e.g., increased risk of GVHD, invasive fungal infection, increased non-relapse mortality).[21] Some form of CMV preventive strategy is recommended for both seropositive recipients and seronegative recipients of seropositive donors in the first 100 days post-transplantation. This can either be in the form of primary prophylaxis or PET.

Currently, most centres use PET, whereby patients are monitored via quantitative PCR or rarely antigenemia on a weekly basis. In general, most institutions in Canada choose to initiate PET in patients with CMV viremia > 1,000 copies/mL. However, some choose to initiate at lower thresholds for higher risk patients. Although intravenous ganciclovir is the only CMV-specific drug with proven efficacy in the prophylaxis setting, it comes with significant toxicity in the form of myelosuppression and, therefore, its preferred use is in a PET setting. Valganciclovir (oral prodrug formulation of ganciclovir) is also used for the management of CMV in a prophylactic setting; however, it has the same toxicity profile as the intravenous formulation of ganciclovir and does not have any randomized trial to support its use as prophylaxis. Overall, PET strategies are reported to have reduced the incidence of CMV disease from a range of 20% to 30% to < 5%, as reported in historical studies.[22] Despite the efficacy of currently available antivirals for the management of CMV, CMV reactivation can still occur and patients are at risk of the indirect effects noted earlier, especially those patients who are high risk for CMV reactivation.

Currently, PET has worked relatively well for reducing the incidence of CMV disease — particularly CMV pneumonia, which had significant mortality.[21] It is not clear if PET has reduced the indirect effects of reactivation and prevention of CMV; however, according to the clinical experts consulted for this review, these benefits would be considered of importance to patients. Letermovir could potentially be used to prevent CMV and its consequences — including both the direct effects of end-organ disease and the indirect effects of reactivation — given that it was studied for prophylaxis and does not have the same myelosuppressive profile as other currently available antivirals; however, letermovir's benefits on these indirect effects are not clear based on the results of Study P001.

According to the clinical experts consulted for this review, it is unlikely that letermovir would be used prophylactically in all allogenic HSCT recipients. This is in part because it is not clear from Study P001 if patients would still require monitoring for reactivation on a weekly basis as they do for PET. If monitoring is still required, then centres will likely not choose to use it broadly for all patients, given the cost and the low incidence of CMV disease with the current strategy of PET. The use of prophylactic treatment would likely be started while a patient is in hospital. This is in contrast to the use of ganciclovir, which is most often given by home care (it is not part of the hospital budget), and therefore patients would transition to an insurer as soon as discharged. Alternatively, coverage could be included as part of transplant case costing (the per transplant amount of money a hospital gets per transplant) through Cancer Care Ontario. However, the clinical experts consulted indicated that this would not likely be on a pan-prophylactic basis.

A more likely scenario for the use of letermovir is in allogenic HSCT recipients who are at higher risk for viral reactivation. The definition of high risk would likely be similar to the criteria used in Study P001 (e.g., umbilical cord blood transplant recipients, haploidentical

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

recipients, recipients of T-cell depleted grafts, recipients requiring high-dose steroids or other immunosuppression for acute GVHD) and patients receiving antithymocyte globulin or Campath (alemtuzumab). These patients have an unmet need given the toxicity of the current prophylaxis and were not excluded from the trial. In Canada, as most unrelated donor transplants use antithymocyte globulin , it is expected that about two-thirds of recipients would be considered high risk for CMV reactivation. According to the clinical experts consulted, the duration of coverage would be approximately 100 days post-stem cell transplant. Patients with prolonged or profound immunosuppression beyond 100 days (e.g., those with severe acute or chronic GVHD) and those who are at higher risk of CMV activation may need continuing prophylaxis and/or monitoring beyond 100 days post-transplant. These patients have an unmet need for either primary or secondary prophylaxis; although letermovir was not studied in this manner, it would likely used for these groups.

Secondary prophylaxis for recipients with CMV disease pre-transplant and considered at risk for a recurrence are another risk group that would benefit from prophylaxis. This may be of particular interest to patients for whom the virus was slow to clear the first time or there were significant issues with ganciclovir therapy (toxicity or not conveniently available for distant patients).These patients have an unmet need but were excluded from this trial. Given that letermovir is suggested to have no cross-resistance to other antivirals, and has no issues with myelosuppression, there could be interest in using letermovir as primary therapy instead of ganciclovir for resistant strains of CMV.

Finally, the largest unmet need currently is for patients requiring therapy who are refractory or resistant to ganciclovir or valganciclovir. These patients often require more toxic drugs (i.e., foscarnet, cidofovir) with varying efficacy. Letermovir was not studied for treatment in these patients; however, letermovir would likely be used for these patients if it were widely available.

Conclusions

The CDR systematic review included one double-blind, phase III, placebo-controlled RCT, Study P001. It was designed to assess the benefits and harms of letermovir compared with placebo as a preventive strategy for clinically significant CMV infection in adults who are CMV-seropositive recipients of an allogeneic HSCT, defined as occurring from either CMV end-organ disease or the initiation of PET based on documented CMV viremia and the clinical condition of the patient.

Letermovir was associated with a statistically significant reduction when compared with placebo for the prevention of clinically significant CMV infection through week 24 post-transplant (primary end point); this was mainly driven by the initiation of PET. The results of secondary end points (clinically significant CMV infection through week 14 post-transplant and the initiation of PET at week 14 and week 24 post-transplant) were supportive of the primary analysis; however, no adjustments for multiple statistical testing were made. There were no statistically significant differences between letermovir and placebo for the occurrence of CMV end-organ disease at 14 and 24 weeks.

A similar percentage of patients in the letermovir arm experienced AEs and serious AEs compared with the placebo arm through weeks 14, 24, and 48 post-transplant. The occurrence of notable harms — specifically, gastrointestinal disorders — was approximately similar in both treatment arms through weeks 14, 24, and 48 post-transplant. Cardiac disorders were more common in patients receiving letermovir compared with placebo through week 14 post-transplant. However, the differences between the two arms diminished through weeks 24 and 48 post-transplant.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

Lymphoma Canada and Myeloma Canada collaborated to produce one patient group submission. Both organizations aim to educate, provide support to, and connect patients (and their respective caregivers) with either lymphoma or myeloma, respectively. Lymphoma Canada has received funding in the past two years from AbbVie, AstraZeneca, Janssen, Lundbeck, Merck, and Seattle. Genetics, while Myeloma Canada has received funding in the past two years from Amgen, Celgene, Janssen, Merck, and Takeda.

Neither organization has any conflicts of interest to declare with regard to this patient input submission.

2. Condition-Related Information

The information obtained for this CADTH Common Drug Review was ascertained through a survey sent out jointly by Lymphoma Canada and Myeloma Canada. It targeted the patient memberships of both organizations. The survey was sent out using social media channels of the Leukemia & Lymphoma Society of Canada and BMT InfoNet. The survey was open from December 13 to 18, 2017, and aimed to ascertain the impact, common experiences, and complications of allogenic stem cell transplants (ASCT) in patients with blood, plasma cell, or lymphoid cancers. It did not specifically ask questions about whether or not the patients were cytomegalovirus (CMV)-positive or whether patients had experience with letermovir. Of the 135 patients who responded to the survey, 103 were eligible to have their responses included in this summary as they had received an ASCT. (Of these 103 patients, 69 were from Canada, 25 were from the US, and the remaining patients were from Europe and Australia.) The majority of patients were over 50 years of age (with only 10% being between the ages of 19 and 40 years) and 51.5% were female. Of the total population, approximately 33% were diagnosed with myeloma, 30% with a type of leukemia, 14% with lymphoma, and the rest with myelodysplastic or myeloproliferative neoplasms. Of those patients who had received ASCT, 82 had one ASCT while three patients had double ASCT. The responses in the following sections are specifically from those patients who received one or more ASCT(s).

After diagnosis with lymphoma, chronic leukemia or acute leukemia, patients typically undergo chemotherapy or targeted therapy. If these treatments fail, then patients are often considered for autologous or ASCT, depending on their disease and eligibility. Patients may start with an autologous stem cell transplant and then they receive an ASCT if the autologous transplant was unsuccessful, depending on their eligibility. Significant symptoms and side effects can be experienced post-ASCT, with the most common AEs being fatigue, weakness, hair loss, and diarrhea. Other symptoms post-ASCT include nausea or vomiting, skin changes, mouth sores, fever, chills, pain, easy bleeding or bruising, constipation, cough or sore throat, and low blood pressure. Of these side effects, 62 patients indicated that the most bothersome were mouth sores or mouth dryness, nausea, fatigue, and pain. Complications experienced by a patient post-ASCT often include infections (bacterial, viral, or fungal), problems with the liver, lung, kidney or heart, and graft failure or rejection. Post-ASCT complications often require patients to use antibiotics, antivirals, antifungals, corticosteroids, and blood transfusions, which are associated with their own side effects. In addition, the added burden of leaving their home or communities in order to receive the

ASCT can also negatively affect patients and their families as the time away can range from one to nine months. The ASCT, in conjunction with its side effects, hospitalization, and time away from homes, can have a significant impact on patient lives, leading to psychological or emotional effects such as problems concentrating, stress, difficulty sleeping, depression, memory loss, anxiety, and lack of sexual desire. According to patients, the most common long-term effects caused by ASCTs included fatigue, peripheral neuropathies, osteoporosis, and cognitive problems. In addition, patients, their caregivers, and families also often experience significant financial burden due to the costs associated with the transplant itself, medications and their administration, travel, accommodation, parking, absence form school or work, or clinical trial charges.

Graft-versus-host disease (GVHD) can also be experienced by patients post-ASCT. Common symptoms experienced by patients with GVHD include skin rash; dry or thickened skin; skin blistering; loss of appetite; nausea or vomiting; weight loss; dry mouth, dry eyes or dry lungs; decreased energy; and jaundice. These symptoms have a significant impact on a patient's daily quality of life. In addition to having GVHD, patients also require additional medication to control it, which can subsequently lead to other side effects such as bloating, immune system weakness, extreme fatigue, and inability to return to work or continue employment. As one patients stated, "I am unable to live a normal life, I'm just surviving at this point," while another patient stated, "No more normal. New normal was slow, painful, and frustrating." When patients experience GVHD, additional visits to the transplant centre for monitoring and/or treatment is indicated. Generally, patients are often readmitted, require longer hospitalization post-ACST, or require emergency department care when they experience GVHD.

3. Current Therapy-Related Information

Lymphoma Canada and Myeloma Canada did not seek information on whether patients were CMV-positive; therefore, no information was provided for this section.

4. Expectations About the Drug Being Reviewed

Lymphoma Canada and Myeloma Canada did not seek information on whether patients were CMV-positive; therefore, no information was provided for this section.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Patient headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 11, 2018
Alerts:	Biweekly search updates until (date of CDEC meeting)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a patient heading
.sh	At the end of a phrase, searches the phrase as a patient heading
MeSH	Medical Patient Heading
fs	Floating subheading
exp	Explode a patient heading
*	Before a word, indicates that the marked patient heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading Word; usually includes patient headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily, and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(Prevymis* or letermovir* or AIC 246 or AIC246 or AIC-246 or MK-8228 or MK8228).ti,ab,kf,ot,hw,rn,nm.
2	(917389-32-3 or 1H09Y5WO1F).rn,nm.
3	1 or 2
4	3 use medall
5	*letermovir/
6	(Prevymis* or letermovir* or AIC 246 or AIC246 or AIC-246 or MK-8228 or MK8228).ti,ab,kw.
7	5 or 6
8	7 use oemezd
9	conference abstract.pt.
10	8 not 9
11	4 or 10
12	remove duplicates from 11

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

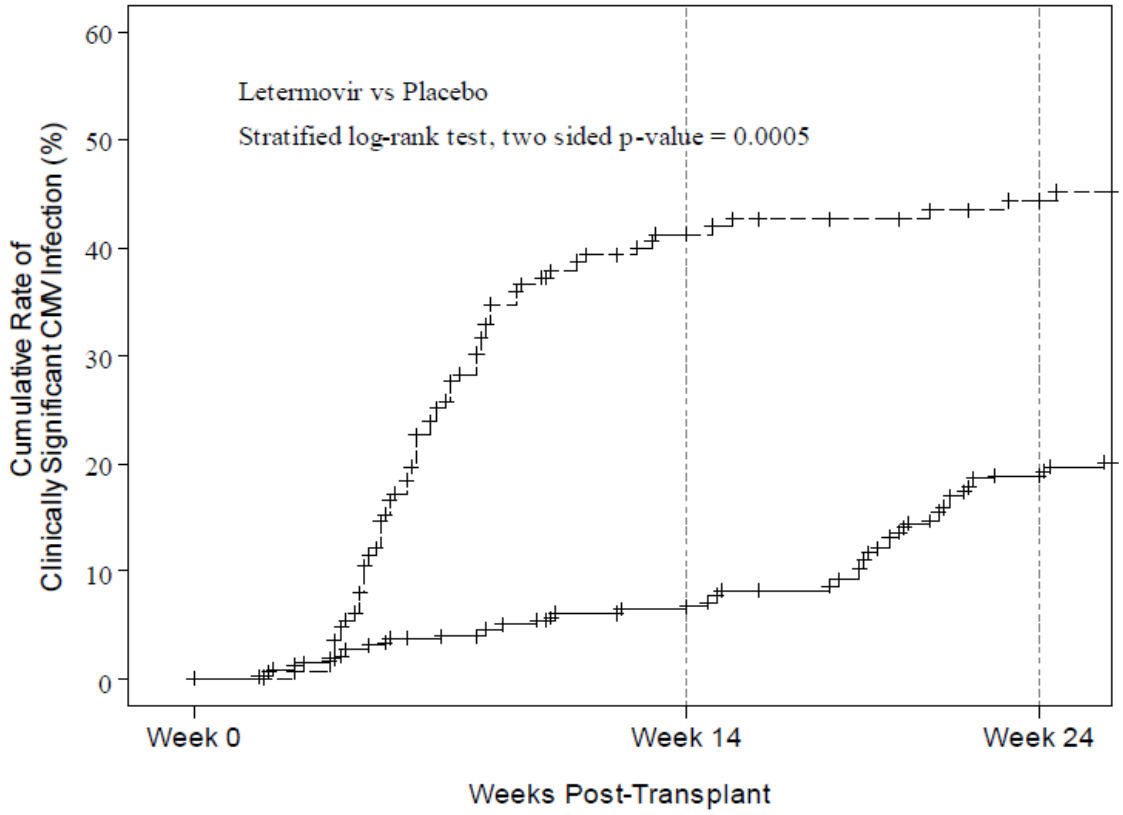
Dates for Search:	January 2018
Keywords:	Prevymis, letermovir, prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey matters: a practical tool for evidence-based searching* (https://www.cadth.ca/resources/finding-evidence/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Detailed Outcome Data

Figure 3: Kaplan–Meier Plot of Time to Onset of Clinically Significant Cytomegalovirus Infection Through Week 24 Post-Transplant (Full Analysis Set)

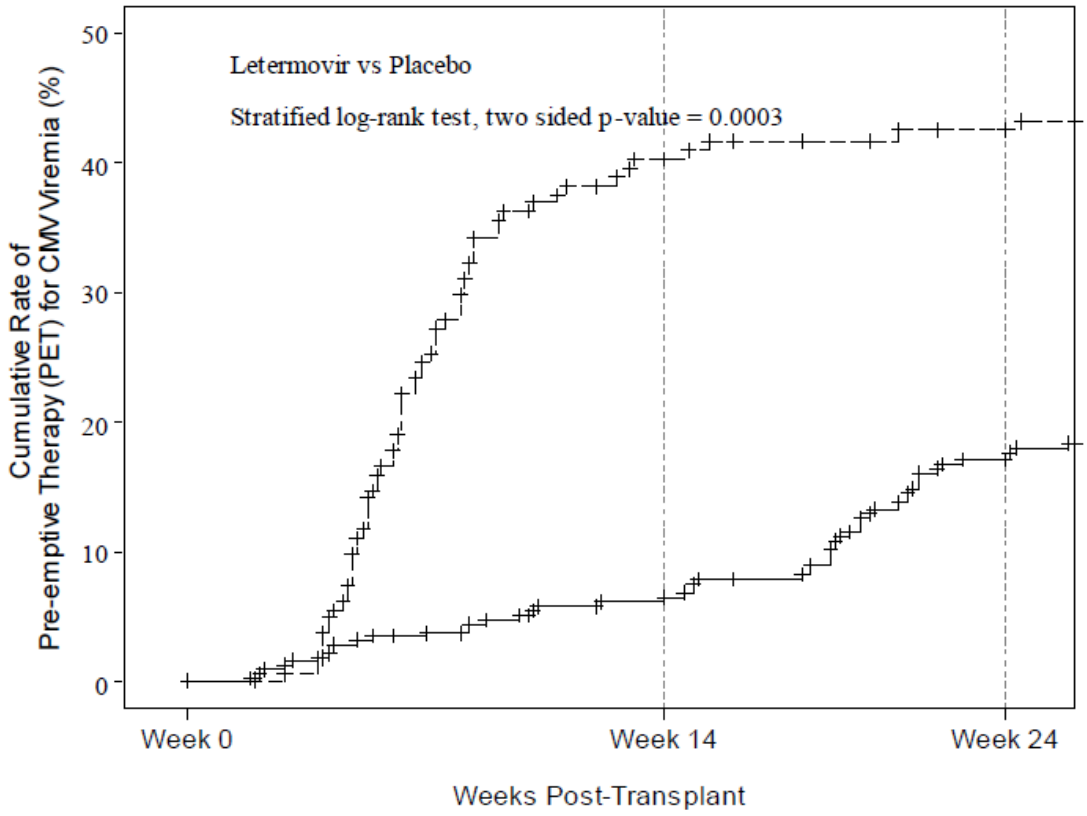


No. at risk: KM estimates % (95% CI)			
Letermovir	325	270: 6.8 (4.0, 9.6)	212: 18.9 (14.4, 23.5)
Placebo	170	85: 41.3 (33.6, 49.0)	70: 44.3 (36.4, 52.1)

CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; KM = Kaplan–Meier.

Source: P001 V01 CSR.[23]

Figure 4: Kaplan–Meier Plot of Time to Initiation of Pre-Emptive Therapy for Cytomegalovirus Viremia Through Week 24 Post-Transplant (Full Analysis Set)

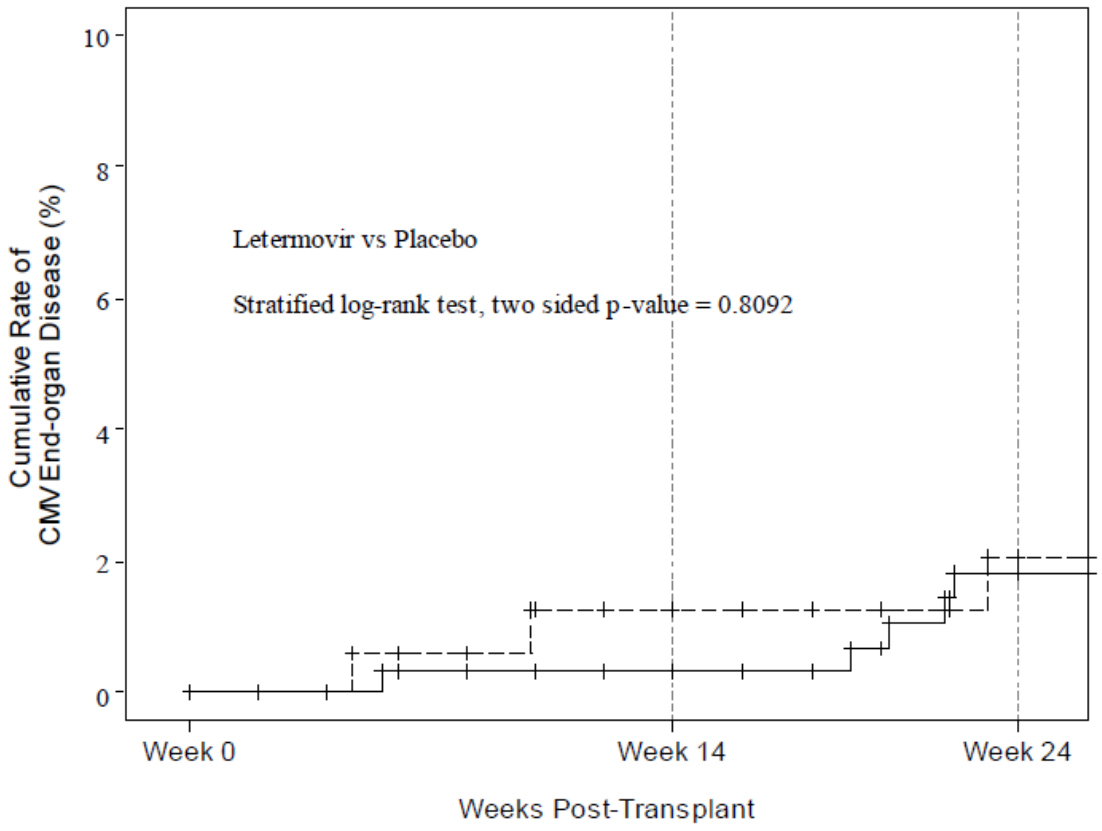


No. at risk: KM estimates % (95% CI)			
Letermovir	325	271: 6.5 (3.7, 9.2)	215: 17.2 (12.8, 21.6)
Placebo	170	86: 40.2 (32.6, 47.9)	72: 42.4 (34.7, 50.2)

CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; KM = Kaplan–Meier; PET = pre-emptive therapy.

Source: P001 V01 CSR.[23]

Figure 5: Kaplan–Meier Plot of Time to Onset of Cytomegalovirus End-Organ Disease Through Week 24 Post-Transplant (Full Analysis Set)

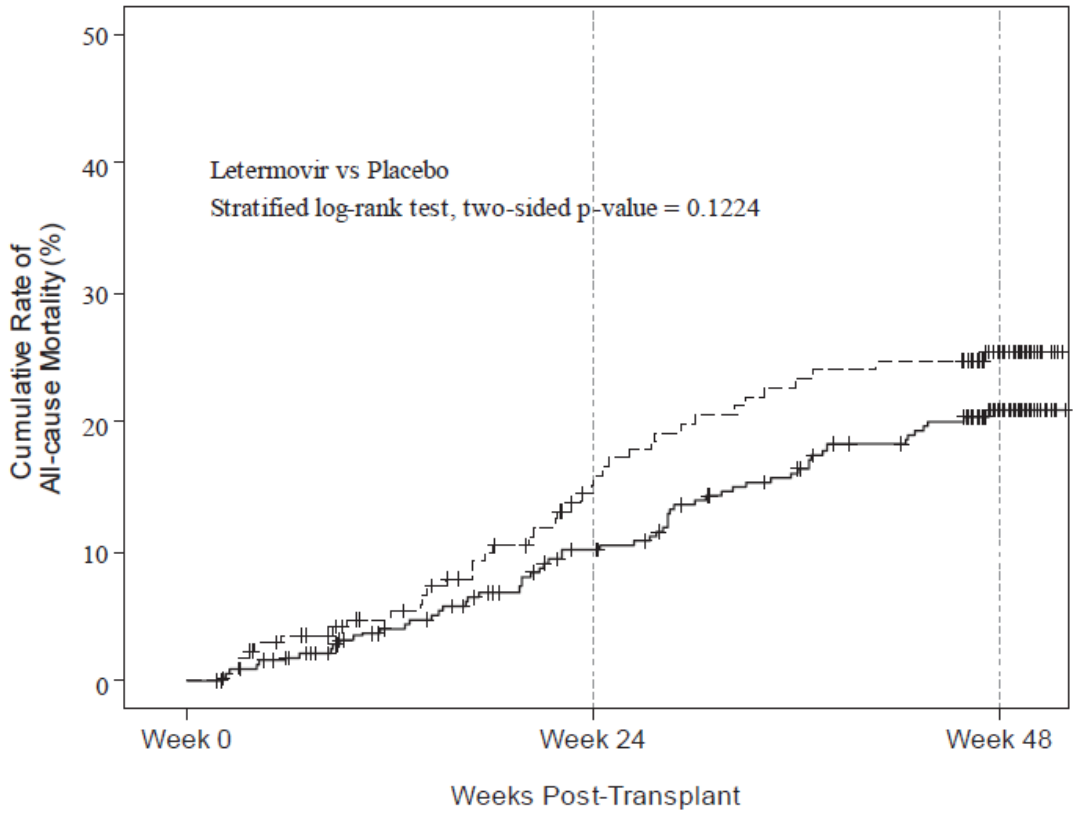


No. at risk: KM estimates % (95% CI)			
Letermovir	325	287: 0.3 (0.0, 1.0)	256: 1.8 (0.2, 3.4)
Placebo	170	145: 1.3 (0.0, 3.0)	118: 2.1 (0.0, 4.4)

CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; KM = Kaplan–Meier.

Source: P001 V01 CSR.[23]

Figure 6: Kaplan–Meier Plot of Time to All-Cause Mortality Through Week 24 and Week 48 Post-Transplant (Full Analysis Set)

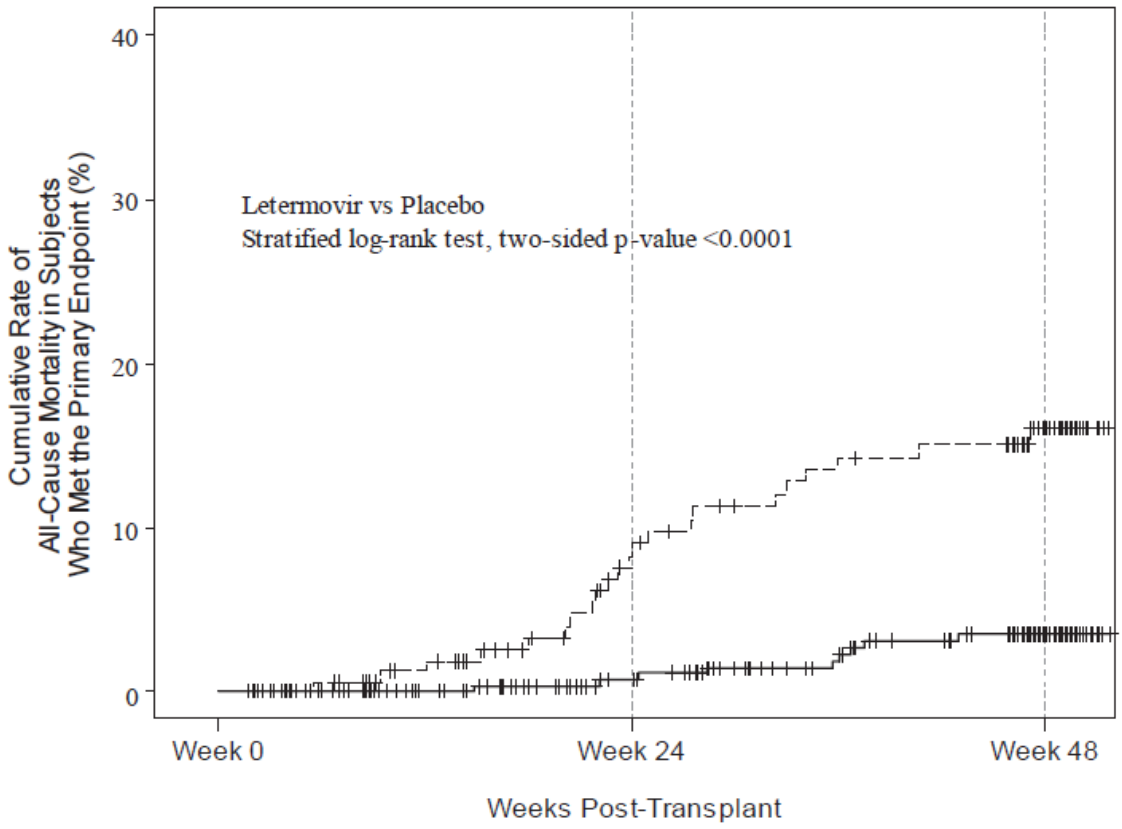


No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 10.2 (6.8, 13.6)	138: 20.9 (16.2, 25.6)
Placebo	170	125: 15.9 (10.2, 21.6)	71: 25.5 (18.6, 32.5)

CI = confidence interval; CSR = Clinical Study Report; KM = Kaplan–Meier.

Source: P001 V02 CSR.[24]

Figure 7: Kaplan–Meier Plot of Time to All-Cause Mortality in Patients Who Met the Primary End Point Through Week 24 and Week 48 Post-Transplant (Full Analysis Set)

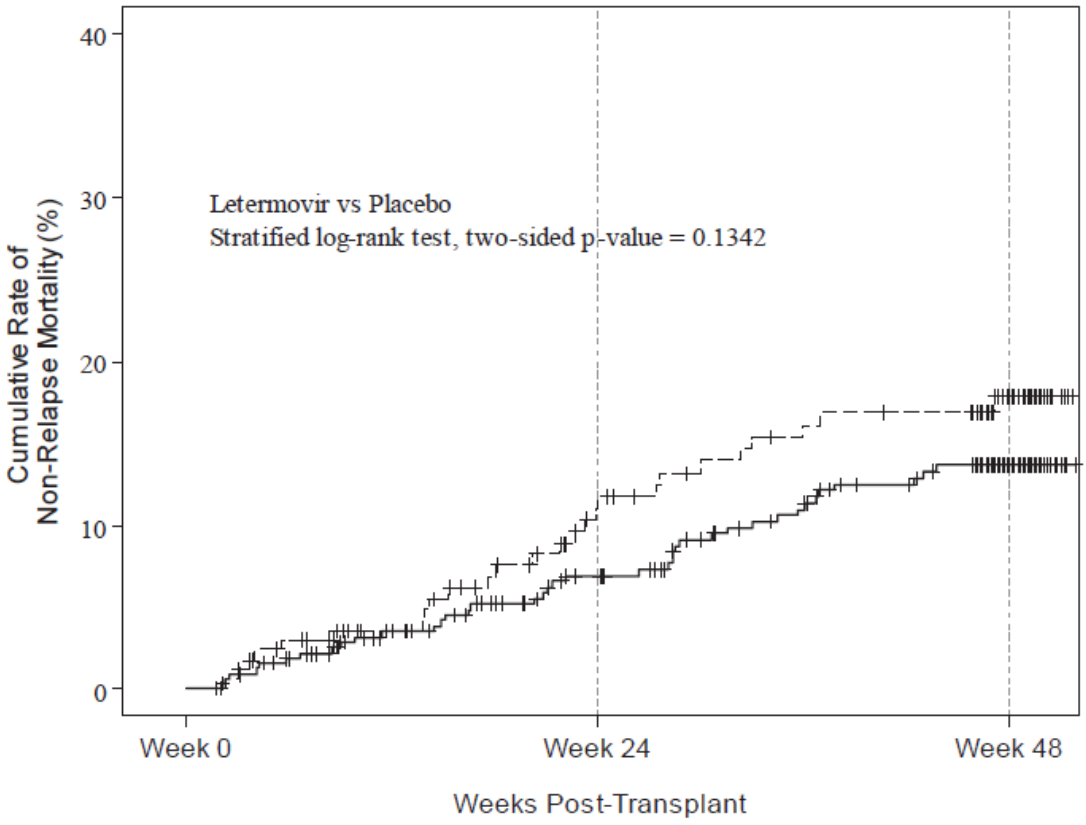


No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 0.7 (0.0, 1.7)	138: 3.6 (1.3, 5.9)
Placebo	170	125: 9.1 (4.3, 13.8)	71: 16.0 (9.9, 22.2)

CI = confidence interval; CSR = Clinical Study Report; KM = Kaplan–Meier.

Source: P001 V02 CSR.[24]

Figure 8: Kaplan–Meier Plot of Time to Non-Relapse Mortality Through Week 24 and Week 48 Post-Transplant (Full Analysis Set)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 6.9 (4.1, 9.8)	138: 13.7 (9.7, 17.7)
Placebo	170	125: 11.7 (6.6, 16.8)	71: 17.8 (11.5, 24.1)

CI = confidence interval; CSR = Clinical Study Report; KM = Kaplan–Meier.

Source: P001 V02 CSR.[24]

Table 22: Summary of Cytomegalovirus Viremia and Through Week 24 Post-Transplant (Full Analysis Set)

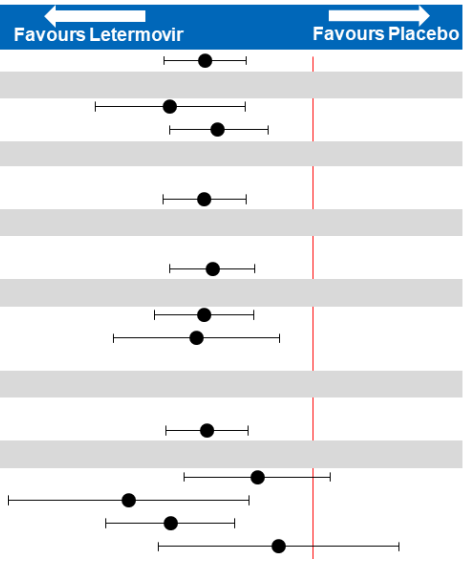
CMV Viremia	Study P001	
	Letermovir N = 325	Placebo N = 170
Patients with CMV viremia, n (%)	186 (57.2)	124 (72.9)
Patients with Clinically Significant CMV Infection	**57 (17.5)**	**71 (41.7)**
Mean maximum CMV DNA, copies/mL (SD)	4,815.4 (11,448.3)	5,150.2 (14,175.9)
Median maximum CMV DNA, copies/mL (min., max.)	405 (150 to 54,654)	1,014 (150 to 106,830)
Category of Maximum CMV DNA (copies/mL) in Patients with Clinically Significant CMV Infection, n (%)		
Detected but not quantifiable	15 (4.6)	13 (7.6)
Quantifiable and < 1,000	23 (7.1)	22 (12.9)
≥ 1,000 and < 10,000	11 (3.4)	27 (15.9)
≥ 10,000	8 (2.5)	9 (5.3)
Patients without Clinically Significant CMV Infection	**129 (39.7)**	**53 (31.2)**
Mean maximum CMV DNA, copies/mL (SD)	285.2 (411.1)	517.7 (1,283.3)
Median maximum CMV DNA, copies/mL (min., max.)	150 (150 to 2,398)	150 (150 to 7,857)
Category of Maximum CMV DNA (copies/mL) in Patients with Clinically Significant CMV Infection, n (%)		
Detected but not quantifiable	101 (31.1)	40 (23.5)
Quantifiable and < 1,000	21 (6.5)	9 (5.3)
≥ 1,000 and < 10,000	7 (2.2)	4 (2.4)
≥ 10,000	0	0

CMV = cytomegalovirus; CSR = Clinical Study Report; max. = maximum; min. = minimum; ; N = total number in the sample under study; n = number in a subgroup of the sample under study; SD = standard deviation.

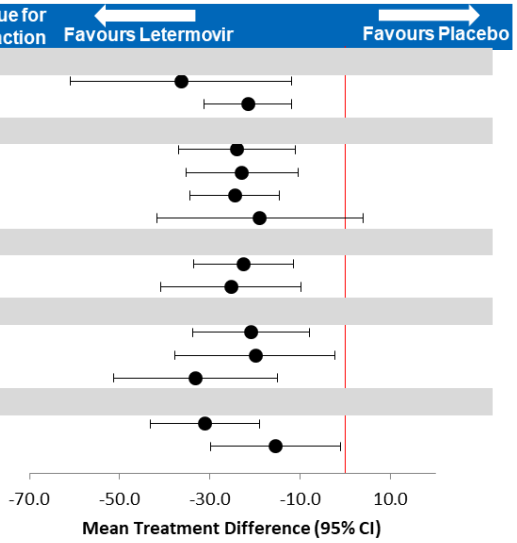
Source: P001 V01 CSR.[23]

Table 23: Primary Efficacy End Point Through Week 24 Post-Transplant and Subgroup Analyses (Full Analysis Set)

Patient Population	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value for Interaction	Favours Letermovir / Favours Placebo
All	122/325 (37.5)	103/170 (60.6)	−23.5 (-32.5, -14.6)	< 0.0001	
Risk[a]				NR	
High	43/102 (42.2)	33/45 (73.3)	−31.2 (-47.5, -14.9)		
Low	79/223 (35.4)	70/125 (56)	−20.9 (-31.3, -9.8)		
Ex Vivo T-Cell Depletion				NR	
Yes	3/9 (33.3)	2/4 (50)	NR		
No	119/316 (37.7)	101/166 (60.8)	−23.7 (-32.8, -14.6)		
Alemtuzumab Use				NR	
Yes	4/11 (36.4)	8/9 (88.9)	NR		
No	118/314 (37.6)	95/161 (59)	−21.9 (-31.2, -12.7)		
Stem Cell Source				NR	
Peripheral blood	84/241 (34.9)	68/117 (58.1)	−23.8 (-34.6, -13.0)		
Bone marrow	31/72 (43.1)	29/43 (67.4)	−25.4 (-43.6, -7.3)		
Cord blood	7/12 (58.3)	6/10 (60)	NR		
GVHD ≥ Grade 2 at Baseline				NR	
Yes	0/1 (0)	1/1 (100)	NR		
No	122/324 (37.7)	102/169 (60.4)	−23.2 (-32.2, -14.2)		
Donor HLA Matching and Relation				NR	
Matched related	40/114 (35.1)	28/59 (47.5)	−12.1 (-28.1, 3.8)		
Mismatched related	16/46 (34.8)	12/16 (75)	−40.2 (-66.5, -13.9)		
Matched unrelated	43/122 (35.2)	49/72 (68.1)	−31.1 (-45.2, -17.1)		
Mismatched unrelated	23/43 (53.5)	14/23 (60.9)	−7.4 (-33.7, 18.8)		



Patient Population	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value for Interaction
Haploidentical				NR
Yes	19/51 (37.3)	14/19 (73.7)	−36.4 (-61.0, -11.8)	
No	103/274 (37.6)	89/151 (58.9)	−21.5 (-31.2, -11.8)	
Age				NR
< median age (55 year)	56/164 (34.1)	48/83 (57.8)	−24.0 (-36.9, -11.0)	
≥ median age (55 years)	66/161 (41)	55/87 (63.2)	−22.9 (-35.3, -10.4)	
< 65 years	100/272 (36.8)	85/139 (61.2)	−24.5 (-34.4, -14.6)	
≥ 65 years	22/53 (41.5)	18/31 (58.1)	−18.9 (-41.7, 3.9)	
Weeks From Transplant to Randomization				NR
< 2 weeks	85/215 (39.5)	68/111 (61.3)	−22.5 (-33.6, -11.5)	
≥ 2 weeks	37/110 (33.6)	35/59 (59.3)	−25.3 (-40.9, -9.7)	
Conditioning Regimen				NR
Myeloablative	60/154 (39)	50/85 (58.8)	−20.9 (-33.9, -7.9)	
Reduced intensity	33/86 (38.4)	28/48 (58.3)	−19.9 (-37.7, -2.2)	
Non-myeloablative	29/85 (34.1)	25/37 (67.6)	−33.2 (-51.4, -15)	
Immunosuppressant Use During Treatment[b]				NR
Cyclosporine A	58/162 (35.8)	60/90 (66.7)	−31.1 (-43.2, -19.0)	
Tacrolimus	56/145 (38.6)	37/69 (53.6)	−15.5 (-29.8, -1.1)	
Other	8/18 (44.4)	5/9 (55.6)	NR	



CI = confidence interval; CSR = Clinical Study Report; GVHD graft-versus-host disease; HLA = human leukocyte antigen; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; NR = not reported; *P* = probability.

Note: The primary analysis included all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window. Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the patient. Ninety-five per cent CIs and *P* value for the treatment differences in per cent response were calculated using stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided *P* value ≤ 0.0249 was used for declaring statistical significance for primary analysis of the primary end point. Nominal one-sided *P* values (not adjusted for multiplicity) are provided for other analyses as a measure of the strength of the relationship between treatment and response. No adjustments for multiple statistical tests were made for any outcomes other than the primary efficacy end point.

[a] High risk is defined as patients meeting one or more of the following criteria at the time of randomization:

- 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, or -DRB1
- use of umbilical cord blood as stem cell source
- use of ex vivo T-cell depleted grafts
- grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥ 1 mg/kg/day of prednisone or equivalent dosage of another corticosteroid).

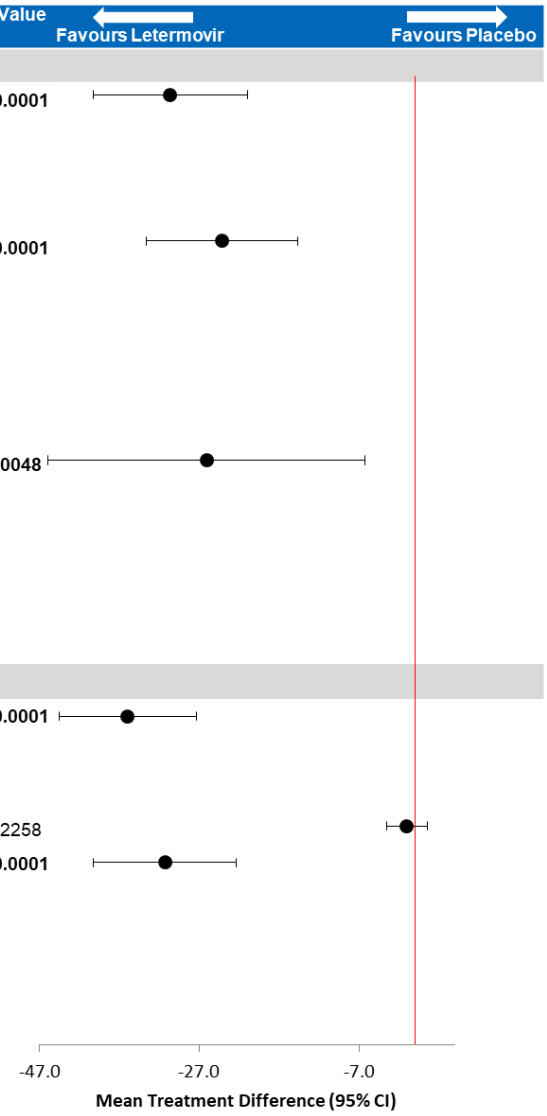
All patients not meeting the definition of high risk were considered low risk.

[b] Patients counted in the cyclosporine A row if they received concomitant cyclosporine A with or without any other immunosuppressants in the regimen during treatment phase. Tacrolimus containing-regimen included concomitant tacrolimus use with or without any other immunosuppressant use (except cyclosporine A). Patients in the other row received a regimen containing any other immunosuppressants (sirolimus, everolimus, systemic steroids, leflunomide, mycophenolate) except cyclosporine A or tacrolimus. The patients in the missing row did not receive any immunosuppressants concomitantly.

Source: P001 V01 CSR.[23]

Table 24: Primary End Point Sensitivity Analyses Through Week 24/14 Post-Transplant

End Point	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value
Week 24 Post-Transplant				
Clinically Significant CMV Infection[cd]	**57/260 (21.9)**	**71/138 (51.4)**	**−30.7 (-40.3, -21.0)**	**< 0.0001**
Clinically significant CMV infection by week 24	57/260 (21.9)	71/138 (51.4)		
Initiation of PET based on documented CMV viremia	5/260 (1.9)	68/138 (49.3)		
CMV end-organ disease	5/260 (1.9)	3/138 (2.2)		
Clinically Significant CMV Infection[abe]	**107/295 (36.3)**	**93/156 (59.6)**	**−24.1 (-33.6, -14.7)**	**< 0.0001**
Clinically significant CMV infection by week 24	50/295 (16.9)	64/156 (41)		
Initiation of PET based on documented CMV viremia	46/295 (15.6)	61/156 (39.1)		
CMV end-organ disease	4/295 (1.4)	3/156 (1.9)		
Discontinued from study before week 24	48/295 (16.3)	24/156 (15.4)		
Missing outcome in week 24 visit window	9/295 (3.1)	5/156 (3.2)		
Clinically Significant CMV Infection[abf]	**31/48 (64.6)**	**20/22 (90.9)**	**−26.1 (-45.9, -6.3)**	**0.0048**
Clinically significant CMV infection by week 24	22/48 (45.8)	17/22 (77.3)		
Initiation of PET based on documented CMV viremia	21/48 (43.8)	17/22 (77.3)		
CMV end-organ disease	2/48 (4.2)	1/22 (4.5)		
Discontinued from study before week 24	8/48 (16.7)	3/22 (13.6)		
Missing outcome in week 24 visit window	1/48 (2.1)	0/22 (0)		
Week 14 Post-Transplant				
Clinically Significant CMV Infection[cd]	25/288 (8.7)	67/152 (44.1)	**−36.0 (-44.5, -27.4)**	**< 0.0001**
Clinically significant CMV infection by week 14	25/288 (8.7)	67/152 (44.1)		
Initiation of PET based on documented CMV viremia	24/288 (8.3)	65/152 (42.8)		
CMV end-organ disease	1/288 (0.3)	2/152 (1.3)	−1.0 (-3.5, 1.5)	0.2258
Clinically Significant CMV Infection[abe]	53/295 (18)	76/156 (48.7)	**−31.3 (-40.3, -22.4)**	**< 0.0001**
Clinically significant CMV infection by week 14	21/295 (7.1)	61/156 (39.1)		
Initiation of PET based on documented CMV viremia	20/295 (6.8)	59/156 (37.8)		
CMV end-organ disease[c]	1/295 (0.3)	2/156 (1.3)		
Discontinued from study before week 14	29/295 (9.8)	13/156 (8.3)		
Missing outcome in week 14 visit window	3/295 (1)	2/156 (1.3)		



CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; *P* = probability; PET = pre-emptive therapy; PP = per-protocol.

Note: Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the patient. Ninety-five per cent CIs and *P* value for the treatment differences in per cent response were calculated using stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided *P* value ≤ 0.0249 was used for declaring statistical significance. No adjustments for multiple statistical tests were made for any outcomes other than the primary efficacy end point.

[a] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[b] The primary analysis included all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through the week 24 post-transplant visit window.

[c] Sensitivity analysis of the primary end point based on observed data only; missing data for a particular end point was excluded from the analysis.

[d] Based on full analysis population.

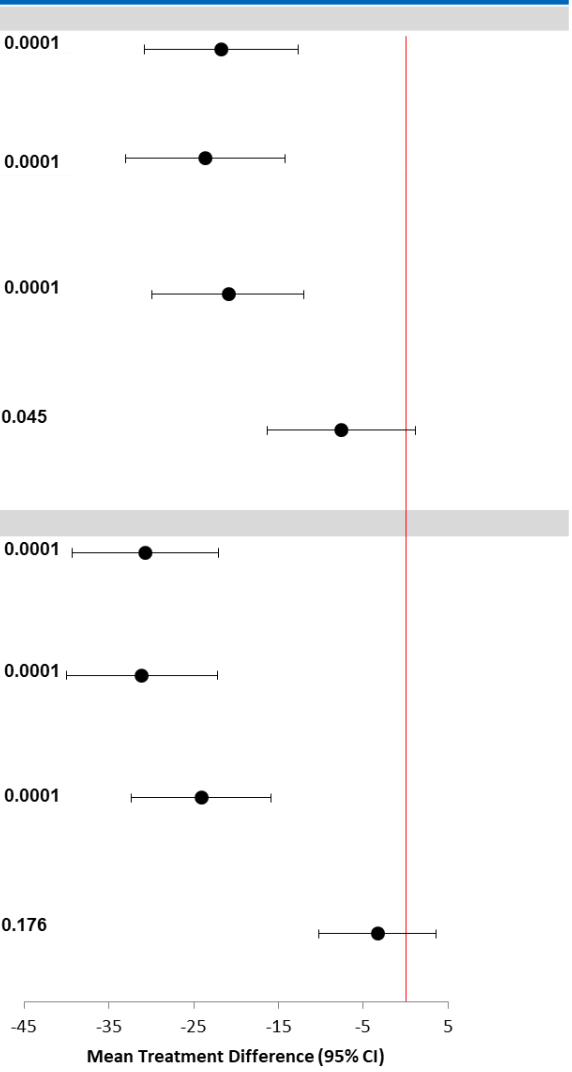
[e] Based on PP population. N = 295 in the letermovir group and N = 156 in the placebo group.

[f] Based on only patients with detectable CMV viral DNA on day 1. N = 48 in the letermovir group and N = 22 in the placebo group.

Source: P001 V01 CSR.[23]

Table 25: Secondary End Point Sensitivity Analyses Through Week 24 and Week 14 Post-Transplant

End Point	Letermovir n/N (%)	Placebo n/N (%)	Stratum-Adjusted MD (95% CI)	*P* Value
Week 24 Post-Transplant				
Initiation of PET[ad]	**124/325 (38.2)**	**101/170 (59.4)**	**−21.8 (-30.8, -12.7)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	57/325 (17.5)	70/170 (41.2)		
Discontinued from study before week 24	57/325 (17.5)	26/170 (15.3)		
Missing outcome in week 24 visit window	10/325 (3.1)	5/170 (2.9)		
Initiation of PET[b]	**105/295 (35.6)**	**91/156 (58.3)**	**23.6 (-33.0, -14.2)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	46/295 (15.6)	61/156 (39.1)		
Discontinued from study before week 24	49/295 (16.6)	25/156 (16.0)		
Missing outcome in week 24 visit window	10/295 (3.4)	5/156 (3.2)		
Initiation of PET[ac]	**98/325 (30.2)**	**86/170 (50.6)**	**−20.9 (-29.9, -12.0)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	29/325 (8.9)	49/170 (28.8)		
Discontinued from study before week 24	59/325 (18.2)	31/170 (18.2)		
Missing outcome in week 24 visit window	10/325 (3.1)	6/170 (3.5)		
CMV End-Organ Disease[b]	**67/295 (22.7)**	**47/156 (30.1)**	**−7.6 (-16.3, 1.2)**	**0.045**
CMV end-organ disease	4/295 (1.4)	3/156 (1.9)		
Discontinued from study before week 24	53/295 (18.0)	35/156 (22.4)		
Missing outcome in week 24 visit window	10/295 (3.4)	9/156 (5.8)		
Week 14 Post-Transplant				
Initiation of PET[ad]	**62/325 (19.1)**	**84/170 (49.4)**	**−30.7 (-39.3, -22.1)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	25/325 (7.7)	67/170 (39.4)		
Discontinued from study before week 14	33/325 (10.2)	15/170 (8.8)		
Missing outcome in week 14 visit window	4/325 (1.2)	2/170 (1.2)		
Initiation of PET[b]	**52/295 (17.6)**	**75/156 (48.1)**	**−31.1 (-40.0, -22.2)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	20/295 (6.8)	59/156 (37.8)		
Discontinued from study before week 14	29/295 (9.8)	14/156 (9.0)		
Missing outcome in week 14 visit window	3/295 (1.0)	2/156 (1.3)		
Initiation of PET[ac]	**49/325 (15.1)**	**66/170 (38.8)**	**−24.1 (-32.4, -15.9)**	**< 0.0001**
Initiation of PET based on documented CMV viremia	11/325 (3.4)	46/170 (27.1)		
Discontinued from study before week 14	34/325 (10.5)	18/170 (10.6)		
Missing outcome in week 14 visit window	4/325 (1.2)	2/170 (1.2)		
CMV End-Organ Disease[b]	**36/295 (12.2)**	**24/156 (15.4)**	**−3.3 (-10.2, 3.6)**	**0.176**
CMV end-organ disease	1/295 (0.3)	2/156 (1.3)		
Discontinued from study before week 14	31/295 (10.5)	17/156 (10.9)		
Missing outcome in week 14 visit window	4/295 (1.4)	5/156 (3.2)		



CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; MD = mean difference; N = total number in the sample under study; n = number in a subgroup of the sample under study; *P* = probability; PET = pre-emptive therapy; PP = per-protocol.

Note: The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed. The primary analysis included all patients who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through week 24 post-transplant visit window. Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the patient. Ninety-five per cent CIs and *P* value for the treatment differences in per cent response were calculated using stratum-adjusted Mantel–Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A one-sided *P* value ≤ 0.0249 was used for declaring statistical significance. No adjustments for multiple statistical tests were made for any outcomes other than the primary efficacy end point.

[a] Based on full analysis population.

[b] Based on PP population. N = 295 in the letermovir group and N = 156 in the placebo group.

[c] Based on per-protocol-recommended viral load threshold.

[d] Includes CMV DNA results from the local laboratory.

Source: P001 V01 CSR.[23]

Table 26: Other Efficacy Outcomes Through Week 24 and Week 14 Post-Transplant (All Patients as Treated)

Outcome	Study P001	
	Letermovir N = 373	Placebo N = 192
Week 14 Post-Transplant, n (%)		
All-cause mortality	20 (5.4)	13 (6.8)
Non-relapse mortality	16 (4.3)	9 (4.7)
CMV-related mortality	1 (< 1)	4 (2.1)
Week 24 Post-Transplant, n (%)		
All-cause mortality	38 (10.2)	29 (15.1)
Non-relapse mortality	24 (6.4)	19 (9.9)
CMV-related mortality	4 (1.1)	16 (8.3)
Week 48 Post-Transplant, n (%)		
All-cause mortality	72 (19.3)	45 (23.4)
Non-relapse mortality	45 (12.1)	29 (15.1)
CMV-related mortality	14 (3.8)	27 (14.1)

CMV = cytomegalovirus; CSR = Clinical Study Report; N = total number in the sample under study; n = number in a subgroup of the sample under study.

Source: P001 V01 CSR,[23] P001 V02 CSR.[24]

Appendix 4: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- EuroQoL 5-Dimensions 3-Level Questionnaire (EQ-5D-3L)
- Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT).

Findings

Table 27: Validity of Outcomes

Instrument	Type	Evidence of Validity	MCID	References

EQ-5D
EQ-5D-3L
	EQ-5D is a general, non–disease-specific health-related quality of life questionnaire. The EQ-5D-3L (version 3L) has:
	• 5 dimensions of health status:
	  ○ mobility
	  ○ self-care
	  ○ usual activities (work, study, housework, and family and leisure activities)
	  ○ pain and discomfort
	  ○ anxiety and depression
	• For each dimension, patient's response could be one of 3 levels:
	  ○ no problems
	  ○ some problems
	  ○ severe problems
	• The digits for the 5 dimensions can be combined in a 5-digit profiler describing the respondent's health state
		Yes: general
		
		BMT specific: unknown
			Various conditions (general use): 0.033 to 0.074 for index score
			
			BMT patients: unknown
				Cheung 2009[64]
				Sinnott 2007[65]

FACT-BMT	Contains the FACT-G (a cancer specific health-related quality of life measure) and additional BMT-specific items. It contains a total of 47 items that are separated into the following domains and scored on a Likert scale: • physical well-being • social and family well-being • relationship with doctor • emotional well-being • functional well-being • additional concerns	Yes	FACT-G: 3 to 7 in cancer patients FACT-BMT: 2-3 points (on the 10-item BMTS scale)	Cella 1993[66] Eton 2004[67] McQuellon 1997[68]

BMT = bone marrow transplant; BMTS = Bone Marrow Transplant Subscale; EQ-5D = European Quality of Life (EuroQoL) Questionnaire; EQ-5D-3L =Level 3 version of EQ-5D; FACT-BMT = Functional Assessment of Cancer Therapy – Bone Marrow Transplant; FACT-G = Functional Assessment of Cancer Therapy – General; MCID = minimal clinically important difference.

EuroQoL 5-Dimensions 3-Level Questionnaire

The European Quality of Life 5-Dimensions (EQ-5D) questionnaire is a generic, health-related quality of life instrument that may be applied to a wide range of health conditions and treatments.[69,70] The first of two parts of the EQ-5D is a descriptive system that

classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The Level 3 version of EQ-5D is EQ-5D-3L. EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing no problems, some problems, and extreme problems, respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions, corresponding with 243 different health states. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[69,70] The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of worst imaginable health state and best imaginable health state. Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for EQ-5D-3L (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than zero represent health states that are valued by society as being worse than dead, while scores of zero and 1.00 are assigned to the health states labelled “dead” and “perfect health,” respectively. Reported minimal clinically important differences (MCIDs) for the EQ-5D-3L version of the scale have ranged from 0.033 to 0.074[65,71] and were derived from patients with a variety of chronic and acute conditions, including rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and acute myocardial infarction. [72,73]

The EQ-5D-3L has been validated[74-76] and found to be a reliable measure[74,77] in various conditions. However, there were no studies identified that reported the reliability, validity, or responsiveness of the EQ-5D-3L in patients who were cytomegalovirus seropositive and who had received an allogeneic hematopoietic stem cell transplant (HSCT). In addition, no MCID for the EQ-5D-3L in this patient population has been identified.

Functional Assessment of Cancer Therapy – Bone Marrow Transplant

The FACT-BMT is a self-assessment tool that is used to measure the quality of life in patients who have received either an autologous or an allogeneic HSCT to treat an underlying hematological condition. The core component of the FACT-BMT is the Functional Assessment of Cancer Therapy – General (FACT-G) component, which was originally developed and validated in cancer patients.[66] It was primarily developed to assess the effects over time of cancer therapy on four major domains; these included physical well-being, emotional well-being, functional well-being, and family and social well-being.[68] A Bone Marrow Transplant Subscale (BMTS) (which, when added to the FACT-G, makes the FACT-BMT instrument) was added to the FACT-G to assess specific concerns related to bone marrow transplant. In order to develop the BMTS, 15 bone marrow transplant patients and seven experts in the field of bone marrow transplants were interviewed. Twelve items

of the BMTS (out of 37 candidate questions) were originally selected to be compatible with version 3 of the FACT-G. However, this eventually went down to 10 items, as two did not highly correlate with the remaining 10 items (i.e., 'I have concerns about my ability to have children' and 'I regret having the bone marrow transplant'). They are not used in the scoring algorithm. The final FACT-BMT has a total of 47 items.[68,78] In terms of scoring, a composite quality-of-life score for the FACT-G is obtained by summing the five subscales. The BMTS subscale has a similar format to the FACT-G and also consists of a Likert-type scale, which ranges from zero to four (zero = not at all, one = a little bit, two = somewhat , three = quite a bit, four = very much).[68] The FACT-BMT includes both subscale scores and an individual score, with higher scores indicating better quality of life.[68] The FACT-BMT total score ranges from zero to 164.[79]

In order to determine the validity and reliability of the FACT-BMT, a prospective longitudinal study was performed on 74 bone marrow transplant patients (including a mix of both autologous [80%] and allogeneic HSCT [20%] who were found not to differ significantly from each other on the FACT-BMT or any of its subscales). Three assessments of the FACT-BMT were performed and consisted of an initial assessment at hospital admission, an assessment at discharge between 18 to 63 days post-transplant, and a follow-up assessment approximately 100 days post-transplant (for which only descriptive statistics were available and for whom there were responses for only 60 patients; five were deceased and five refused to participate). Therefore, complete data were available for 60 patients. In order to examine construct validity, three additional instruments were used alongside the FACT-BMT: the brief Profile of Mood States — Total Mood Disturbance Scale, the Center for Epidemiological Studies-Depression screen scale, and the Medical Outcomes Study-Social Support survey. Alpha coefficients ranging from 0.54 to 0.63 were obtained for the 10-item scale, suggesting acceptable internal consistency with the alpha coefficient for the total FACT-BMT ranging from 0.85 to 0.92.[68] Sensitivity to change of the BMTS portion was evident and more detailed when compared with The Eastern Cooperative Oncology Group performance status rating (ECOG-PSR). The majority of patients (50 out of 74) reported post-transplant decreases in their performance status rating, with a mean BMTS (10 item) score change of −3.3 points (standard deviation of 4.4) (n = 50) and a mean change of −0.5 points (standard deviation of 5.3) (n = 23) in patients with a performance status rating that remained the same or improved. This provides evidence of the sensitivity of the BMTS.[68] In addition, statistically significant changes in the expected direction at the three time points (decreasing at discharge and nearing baseline rates at 100 days post-transplant) were also observed in four subscales on the FACT-BMT and indicated sensitivity to change.[68] (The four subscales on the FACT-BMT were physical well-being, functional well-being, BMTS, and the Trial Outcome Index, itself consisting of the physical well-being, functional well-being and 10-item BMTS combined). The FACT-BMT has also been translated and validated in other languages.[79-82]

In order to ascertain if there were differences between instruments used to measure the quality of life of 56 patients who received bone marrow transplants (both autologous and allogeneic), Kopp et al.[78] compared the European Organisation for Research and Treatment of Cancer quality of life questionnaire with the FACT-BMT — two questionnaires often used in this population. It appeared that there was a significant correlation between the European Organisation for Research and Treatment of Cancer global quality of life score and the FACT-G score (Spearman correlation coefficient of 0.77, $P \leq 0.001$). This was high enough to infer that they address similar issues.[78] In addition, there were also high correlations between certain corresponding subscales. However, the authors were surprised to find even higher correlation with non-corresponding subscales (e.g., physical

well-being of the FACT-BMT and the global quality-of-life score of the European Organisation for Research and Treatment of Cancer questionnaire; 0.82). The authors also found poor correlations between the emotional dimensions (0.30) and social dimensions (0.38) of the two instruments.[78] Therefore, the authors caution that the quality-of-life instrument option are vital and that there are certain advantages of using disease-specific (rather than general) instruments, like that of the FACT-BMT.[78] They also advised that the European Organisation for Research and Treatment of Cancer quality of life questionnaire may be more beneficial to use when wanting to focus on physical and functional symptoms along with side effects, and the FACT-BMT more beneficial to use when more detailed information is needed. In addition, the FACT-BMT provides a global score that integrates all of the quality-of-life dimensions (which may be more pertinent when obtaining integrated data from longitudinal and follow-up studies).[78]

In terms of the MCID, a change of one or more points on the ECOG-PSR is considered clinically important.[68] A mean change of two to three points on the 10-item BMTS is associated with a change in one point in the ECOG-PSR; therefore, an MCID of two to three points on the FACT-BMT subscale may be considered clinically meaningful.[68]

Conclusion

The EQ-5D-3L is a general, non–disease-specific health-related quality-of-life questionnaire. While it has been validated in many conditions, there is no evidence that this tool has been examined in cytomegalovirus-seropositive patients who have received a hematopoietic stem cell transplant. In addition, while an MCID of 0.33 to 0.074 (index score) for various conditions (general use) has been obtained, there is no evidence of an MCID in patients receiving allogeneic HSCT.

The FACT-BMT was validated and found to be both reliable and sensitive to change in patients who had received either autologous or allogeneic HSCT. In terms of the MCID, a change of one or more points on the ECOG-PSR is considered clinically important.[68] A mean change of two to three points on the 10-item BMTS is associated with a change in one point in the ECOG-PSR. Therefore, an MCID of two to three points on the FACT-BMT may be considered clinically meaningful.[68]

Appendix 5: Cobas AmpliPrep/Cobas Taqman Cytomegalovirus Test

Aim

To summarize information pertaining to the Cobas AmpliPrep/Cobas TaqMan Cytomegalovirus Test (CAP/CTM CMV).

Findings

The CAP/CTM CMV was the first commercially available polymerase chain reaction (PCR) test that was approved by FDA for cytomegalovirus (CMV) viremia monitoring in hematopoietic stem cell transplant recipient patients.[83,84] In order to detect and amplify CMV, a 362 base pair sequence primer of the UL54 polymerase gene of CMV is used. Analytically using real-time PCR, the CAP/CTM CMV has demonstrated excellent precision and accuracy, showing a tenfold improved lower limit of detection when compared with the Cobas Amplicor CMV test (another standardized CMV detection test).[85] It has been also determined to be more sensitive than pp65 antigenemia and conventional PCR assays.[85] In addition, when compared with the Cobas Amplicor CMV test, the CAP/CTM CMV has an increased linear range, is more sensitive, has an improved CMV detection rate (hence, it is more suitable for detecting low levels of CMV), and is associated with reduced hands-on time and contamination risk.[84,85] Its large capacity and shorter turnaround time make the CAP/CTM CMV suitable for large centres. However, the Cobas Amplicor is large (3.0m x 0.8m) and a larger sample volume is required (2.5 times larger sample size compared with other tests).[84,85]

The main concerns in this area of medicine is the inter-laboratory and inter-assay variability.[83-85] This led the World Health Organization to release an international standard for CMV quantification (IU/mL) in 2010, which permits direct comparison between assays and laboratories.[83,84] CAP/CTM CMV was the first assay that was calibrated to this World Health Organization standard.[84]

The CAP/CTM CMV is currently marketed for quantifying CMV viral load in plasma samples[83,84] and not in whole blood samples; however, many laboratories still use whole blood cells for their analyses. In one study that compared CAP/CTM CMV to the MagNA Pure instrument (both manufactured by Roche Diagnostics) using whole blood samples, CAP/CTM CMV was observed to have 100% specificity, high linearity range, and a detection limit of 150 copies/mL (2.2 $\log_{10}$ copies/mL).[86] In studies that have compared plasma to whole blood samples, the authors have noted that higher viral loads were generated using the CAP/CTM CMV with whole blood samples. However, the most probable reason for this is the presence of both cell-associated and free CMV in whole blood.[83,84] This assay was observed to have increased sensitivity in plasma samples, especially in instances where there were lower CMV viral levels.[83,84]

According the manufacturer's specifications, the lower limit of CMV detection using the CAP/CTM CMV on plasma samples is 91 IU/mL (95% detection rate), with the lower and upper limits of quantification being 137 IU/mL and 9,100,000 IU/mL, respectively.[83] Therefore, CMV quantification in plasma samples is possible between 137 and 9,100,111 IU/mL, with levels between zero and < 137 IU/mL and > 9,100,000 IU/mL being detectable but not quantifiable.[83,84] The authors of one study recommend using plasma samples when

using CAP/CTM CMV (as per the manufacturer's specifications) in hematopoietic stem cell transplant recipients and proposed an initial viral load threshold of 1,350 IU/mL when distinguishing between asymptomatic CMV infection and CMV disease (this based on a sensitivity of 89% and a specificity of 87%).[83]

Conclusion

The CAP/CTM CMV test alongside real-time PCR is a precise and accurate CMV test when using plasma samples. The lower and upper limits of quantification are 137 IU/mL and 9,100,000 IU/mL (with CMV levels being detectable below and above the quantification levels still being detectable).

Appendix 6: Correlation of Cytomegalovirus Viral Load and Clinical Outcomes

Aim

To summarize information regarding the association between cytomegalovirus (CMV) viral load anytime post-allogeneic hematopoietic stem cell transplant (HSCT) and future CMV morbidity or mortality.

Findings

Patients who have undergone allogeneic HSCT are at risk for the development of a multitude of infections, particularly CMV. Morbidity and mortality related to CMV infection are concerns in this patient population and there is a need to determine predictive factors that will provide insight into if, when, and how these outcomes will manifest. Determining the predictive value of viral loads post-transplant may aid in the successful treatment of CMV disease and CMV infection or circumvention of the development of CMV disease.[59] Previous evidence has indicated that viral load is important at predicting early CMV disease in patients who have received HSCT;[87] however, late-developing CMV disease is also an important concern as the morbidity and mortality associated with it is significant.[57,59]

Many studies have examined the association between risk factors and the development of CMV disease in patients receiving antiviral pre-emptive treatment (PET).[57,58,60] A prospective study by Green et al.[57] included a large cohort of patients who had received their first allogeneic HSCT and who were at risk for CMV disease (either themselves seropositive or having received a transplant from a seropositive donor). The authors examined the efficacy of pp65 antigenemia as well as quantitative polymerase chain reaction (PCR) for the detection of CMV infection and the use of these surveillance techniques to initiate PET with either ganciclovir or foscarnet, based on antigenemia results of more than one positive cell per two slides or a CMV viral load of ≥ 500 copies/mL or a fivefold increase from baseline within the previous month. The authors observed that 33 of the 41 cases of CMV disease that occurred within the first 100 days post-transplant occurred without a positive pp65 antigenemia test (n = 690), whereas four of 19 patients (n = 367) in the risk-adapted quantitative PCR cohort occurred without a positive PCR test. Seven of the 19 patients in the PCR cohort were diagnosed with CMV disease after more than four days of PET and there were eight patients whose treatment started less than 48 hours before CMV disease diagnosis, given that the PCR level was below treatment threshold.[57] After 100 days post-transplant, a PCR viral load of ≥ 1,000 copies/mL (or a viral load fivefold increase within one month) was used to guide PET. In patients who developed late CMV disease (> 100 days post-transplant), six of 13 patients were positive in their PCR surveillance test (with a viral load range of between 36 to 660 copies/mL) before disease development.[57] In terms of mortality, any level of CMV infection detected by either pp65 antigenemia or PCR was associated with a 61% increase in the probability of death without relapse, with this probability increasing to 84% if the levels were above the PET treatment threshold of ≥ 1,000 copies/mL.[57] Given that 46% of late CMV disease occurred in patients with multiple positive PCR tests prior to their CMV disease diagnosis, the authors questioned whether a lower threshold might be more appropriate for the prevention of late disease.[57] The main limitation associated with this study was its observational design.[57]

Furthering their previous research, Green et al.[60] went on to retrospectively examine the association of CMV viral load using the World Health Organization standard international units, or IU/mL, with non-relapse mortality and overall mortality in the first year post-HSCT (n = 926). Most patients were initiated on PET when their viral loads reached 125 UI/mL unless they were considered high risk (on at least 1 mg/kg body weight of prednisone or cord blood HSCT recipients, in which case they started PET after any positive viral load). The authors noted that a significantly increased risk of death from any cause was observed in patients with CMV viral loads of > 500 IU/mL, with the highest risk observed in the first 60 days post-HSCT in patients whose viral loads were 500 to 1,000 and > 1,000 IU/mL. This featured a hazard ratio (HR) of 21.3 (95% confidence interval [CI] of 5.9 to 76.6) and a HR of 26.5 (95% CI of 10.3 to 68.0), respectively.[60] In terms of non-relapse mortality, a positive dose-response relationship was observed in the adjusted HRs for the following viral loads: any positive to 500 IU/mL (HR of 1.3 [95% CI of 0.9 to 2.0]), 500 to 1,000 IU/mL (HR of 2.5 [95% CI of 1.3 to 4.7]), and > 1,000 IU/mL (HR of 4.6 [95% CI of 2.8 to 7.5]).[60] Due to the aforementioned results, the authors determined that higher CMV viral loads are associated with an increased risk of both overall mortality and non-relapse mortality within the first year post-HSCT. In addition, a 20-fold increase in the risk of death by 60 days post-HSCT was observed in patients with viremia of > 500 IU/mL; however, this risk significantly diminished after day 60.[60] A limitation associated with this study included the high-risk nature of the included patients.[60]

Jang et al.[58] examined the risk factors for the progression of CMV viremia to CMV disease in 114 Korean patients who received allogeneic HSCT and were receiving PET. These patients received PET with ganciclovir 5 mg/kg if their viral load exceeded 5,000 copies/mL or their qualitative PCR results were positive in two consecutive tests. CMV disease occurred at a median of 130 days post-allogeneic HSCT, with 34 episodes being detected after 100 days. When compared with patients who experienced a lower initial CMV viral load (≤ 20,000 copies/mL), patients with a higher initial CMV viral load (> 20,000 copies/mL) and lymphopenia on day 100 post-allogeneic HSCT were observed to have greater CMV disease progression (38% > 20,000 copies/mL versus 11.4% ≤ 20,000 copies/mL; *P* =0.008).[58] In this cohort, early CMV viremia was not a significant risk factor for the progression of CMV viremia to CMV disease. However, limitations with this study include the small sample size, the retrospective analysis, and the thresholds that were much larger than that used in North American clinical practice (according to the expert consulted on this review).[58]

In order to examine the effects of viral load and viral load kinetics on the risk of CMV disease, Ljungman et al.[63] looked at 162 patients who were CMV-seropositive, who had allogeneically received stems cells from seropositive donors or who were donor and recipient CMV-positive. Patients in this cohort received PET when they had a viral load of 100 genome copies / 200,000 cells as determined by PCR (using peripheral blood lymphocytes for their analysis). In terms of donor and recipient CMV-positive serological status prior to stem cell transplant and how that affected viral load, the results were statistically significant when comparing CMV-positive recipients, with both the donor and recipients being CMV-positive (mean $\log_{10}$ DNA copies of 3.0 [standard error, or SE] of 0.16; *P* = < 0.05). This was also observed when comparing CMV-positive donors with both the donors and recipients who were CMV-positive (mean $\log_{10}$ DNA copies of 2.6 [SE of 0.10]).[63] When comparing patients who developed CMV disease to those who did not, the peak viral loads in the first episode of CMV-DNAmeia were observed to be higher ($\log_{10}$ of 3.5, SE of ± 0.26 compared with $\log_{10}$ 2.7, SE of ± 0.09; *P* =0.02, respectively).[63] However, this did not correspond to the viral load at diagnosis of CMV disease, as these viral loads

were lower due to the initiation of PET (log_{10} 2.9, SE of ± 0.25). Thus, there were no observed viral load differences between patients who did and did not develop CMV disease.[63]. In addition, the authors did not observe as high an incidence of late CMV disease in their cohort when compared with other studies. In their patient cohort, only acute graft-versus-host disease (GVHD) and the use of corticosteroids were correlated with the development of CMV disease.[63] Limitations associated with this study are the small sample size and the fact that they only performed PCR on peripheral blood lymphocytes instead of performing on both peripheral blood lymphocytes and whole blood (which was done in other studies).[63]

Tan et al.[62] retrospectively examined the relationship of CMV DNA plasma levels at PET initiation, the time to viremia resolution, and the PET duration in 256 HSCT patients with a positive PCR test result. Episodes were separated into three viral load groups at initiation of PET — 135 to 440 IU/mL, 441 to 1,000 IU/mL, and >1,000 IU/mL, in which PET was initiated in 89, 104, and 112 episodes, respectively. Lower viral loads at PET initiation were associated with significantly shorter median time to viremia resolution (15, 18, and 21 days for 135 IU/mL to 440 IU/mL, 441 IU/mL to 1,000 IU/mL, and >1,000 IU/mL, respectively), with adjusted HR for shortened viremia duration of 1.35 (95% CI, 1.02 to 1.79; *P* =0.03) for the 441 IU/mL to 1,000 IU/mL group and 2.10 (95% CI, 1.55 to 2.85; *P* < 0.001) for the 135 IU/mL to 440 IU/mL group when the > 1,000 IU/mL was used as the reference.[62] Prolonged viremia that lasted more than 30 days occurred less frequently in the lower viral load groups (135 IU/mL to 440 IU/mL, 441 IU/mL to 1,000 IU/mL, and > 1,000 IU/mL being 1% vs. 15% vs .24%, respectively; *P* <0.001). The treatment duration was also observed to be significantly shorter in the lower viral load groups (28, 34, and 37 days, respectively; *P* <0.001).[62] Therefore, this study highlights that lower CMV viral loads were associated with shorter viremia episodes, a decreased risk for viremia lasting longer than 30 days, and shorter duration of treatment. One important consideration that the authors noted was the fact that some of the CMV viremia that were treated at the lower viral loads may have resolved spontaneously, thus exposing patients to potentially unwanted AEs associated with PET. In addition, limitations in this study included no specific treatment protocols (as physicians were allowed to choose their antiviral agent, the dosage, and titration), no drug level monitoring, and the retrospective nature of the study.[62]

In a prospective study of 146 consecutive CMV-seropositive patients who had undergone their first allogeneic marrow transplant, had no relapse of their leukemia, and had been tested for CMV (using CMV pp65 antigenemia and CMV DNA by PCR) between 80 and 200 days post-transplantation or until CMV disease detection, Boeckh et al.[59] determined that late CMV disease was predicted by both immunologic and viral factors. They noted that one of the strongest risk factors for late CMV disease (using univariate analysis) was CMV antigenemia during the first three months post-transplant (along with low CD4 counts, delayed lymphocyte engraftment, and GVHD).[59] In addition, the authors observed a strong association (that was independent of CMV disease, GVHD, lymphopenia, and CMV-specific T-cell function) between late death and virologic factors.[59] The main limitation regarding this study is the fact that the aforementioned was observed in patients who had undergone myeloablative transplantation and, therefore, may not be generalizable to patients who have received non-myeloablative transplantation.[59]

Patients having received allogeneic HSCT and experienced CMV viremia are at an increased risk of infection with opportunistic invasive fungal diseases (IFD). IFD complications are difficult to diagnosis, are associated with high mortality, and are treated with toxic drugs for long durations.[61] Yong et al.[61] retrospectively studied a cohort of 419

patients at two different centres. Thirty-eight of these patients developed IFD, with an overall incidence of IFD post-allogeneic HSCT of 9.1%. Compared with patients who did not have CMV infection, patients with CMV infection had a higher incidence of IFD (15% versus 7%; *P* = 0.012); however, there was no association between a viral load above or below the median peak CMV viral load (2,689 versus 2,576 IU/mL; *P* = 0.2) and IFD.[61] Limitations associated with this study are the retrospective nature of this study and the lack of information on immunosuppressive agents (particularly corticosteroid and ganciclovir use), which can ultimately increase the pre-disposition of the patient to IFD.[61]

Conclusion

It appears that there is a correlation between viral load and negative outcomes, including the development of CMV disease, bacteria and /fungal infections, and mortality. There is no consensus between the aforementioned identified studies regarding the exact viral load that determines the increase risk of progression from CMV viremia to CMV disease; this is probably due to the differences between viral load thresholds and the different time points examined in the individual studies.[57-60] One of the identified studies did not support the correlation between high viral load and the development of CMV disease;[63] however, most studies reported that higher viral loads or CMV viremia at PET initiation were indicative for the development of CMV disease,[57,58] late CMV disease,[59] and an increase in overall mortality and non-relapse mortality.[60] Lower CMV viral loads have been observed to be associated with shorter viremia episodes, decreased risk for viremia lasting longer than 30 days, and shorter duration of treatment [62] and infection of CMV post-allogeneic HSCT. An increased risk in the development of IFD was observed with infection of CMV post-allogeneic HSCT.[61] While the aforementioned studies have provided evidence that viral load is an important measure that requires attention when treating patients post-allogeneic HSCT, there were limitations associated with each study (such as the retrospective nature of the studies and differences in the patient populations), which should be taken into consideration.

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