CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209939Orig1s000
209940Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	209939 and 209940
Priority or Standard	Priority
Submit Date(s)	March 8, 2017
Received Date(s)	March 8, 2017
PDUFA Goal Date	November 8, 2017
Division/Office	DAVP/OAP
Reviewer Name(s)	Aimee Hodowanec
Review Completion Date	August 7, 2017
Established Name	Letermovir
(Proposed) Trade Name	Prevymis
Applicant	Merck
Formulation(s)	240 mg tablets, 480 mg tablets, 240 mg/12 mL vial, and 480 mg/24 mL vial
Dosing Regimen	480 mg PO or IV once daily until 100 days post-transplantation
Applicant Proposed Indication(s)/Population(s)	Prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
ANC	absolute neutrophil count
ASaT	all subjects as treated
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CDV	cidofovir
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
CRF	case report form
CRT	clinical review template
CsA	cyclosporine
CSR	clinical study report
DAIDS	Division of AIDS
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FAS	full analysis set
FDA	Food and Drug Administration
FOS	foscarnet
GCP	good clinical practice
GCV	ganciclovir
GI	gastrointestinal
GVHD	graft versus host disease
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application

NME	new molecular entity
NOAEL	no observed adverse effect level
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCR	polymerase chain reaction
PD	pharmacodynamics
PET	preemptive therapy
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SMQ	standardized MedDRA query
SOC	system organ class
SOT	solid organ transplant
TEAE	treatment emergent adverse event
VGCV	valganciclovir

1 Executive Summary

1.1. Product Introduction

Letermovir is a new molecular entity (NME). It is an antiviral agent with activity against human cytomegalovirus (CMV) with a novel mechanism of action, targeting the CMV terminase complex. Letermovir comes in an oral (tablet) and an intravenous (IV) formulation and separate new drug applications (NDAs) have been submitted simultaneously for each formulation.

The proposed indication for letermovir is (b) (4) of CMV infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). The recommended dosage of letermovir is 480 mg orally or IV once daily, or 240 mg orally or IV once daily if the patient is receiving cyclosporine, through 100 days post-transplant.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This Application contains substantial evidence of effectiveness as required by law 21 CFR 314.126(a)(b) to support approval of letermovir for the (b) (4) of CMV infection or disease in HSCT recipients. This evidence comes from a Phase 3 trial, Trial P001, and a Phase 2b trial, Trial P020. Trial P001 was a large, randomized, double blind, placebo-controlled trial in which letermovir was robustly shown to reduce the incidence of clinically significant CMV infection in HSCT recipients through Week 24 post-transplantation. Trial P020 was a randomized, double-blind, placebo-controlled trial in which HSCT recipients received one of three letermovir doses or placebo for prophylaxis of CMV infection. Although Trial P020 used letermovir doses which were lower than the to-be-marketed dose, the trial demonstrated a dose-dependent decrease in CMV prophylaxis failure among subjects receiving letermovir. The endpoints 'clinically significant CMV infection' and 'CMV prophylaxis failure' are both composite endpoints with clinical (CMV end-organ disease) and virologic (CMV viremia leading to preemptive CMV treatment) components. In both trials, CMV end-organ disease was uncommon, due to the use of preemptive therapy (treatment of asymptomatic CMV viremia, which is considered standard of care in this population). Therefore, the success of letermovir was based primarily on the prevention of CMV viremia. Importantly, letermovir also demonstrated a reduction in all-cause mortality at Week 24 post-transplant in Trial P001. Therefore, although CMV viremia is currently considered an unvalidated surrogate endpoint, reasonably likely to predict clinical benefit, the reduction in all-cause mortality combined with a highly statistically significant reduction in CMV viremia provide support for a traditional approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Letermovir is an inhibitor of the cytomegalovirus (CMV) terminase complex. This is a novel mechanism of action and therefore cross-resistance with other currently available anti-CMV drugs is not anticipated. The proposed indication for letermovir is the (b) (4) of CMV infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

It is estimated that 40-100% of adults worldwide have been exposed to CMV. Like other herpes viruses, following primary infection, CMV establishes a lifelong infection. While this chronic infection is generally latent and asymptomatic, persons with compromised immunity are at increased risk for CMV reactivation. CMV reactivation among allogeneic HSCT recipients is associated with significant morbidity and mortality. Approximately 27,000 allogeneic HSCTs are performed each year and this number is expected to rise. Among CMV seropositive allogeneic HSCT recipients, up to 80% will experience CMV infection in the absence of prophylaxis. CMV infection in HSCT recipients may manifest as CMV viremia with associated fever and laboratory abnormalities; or as end-organ disease, potentially involving the gastrointestinal tract, liver, lungs, and other organ systems. In the absence of treatment, it is estimated that approximately 30% of HSCT recipients who develop CMV viremia will develop CMV end-organ disease. CMV end-organ disease, CMV pneumonia in particular, is associated with significant mortality.

Due to the potential morbidity and mortality associated with CMV reactivation, it is recommended that all at-risk transplant recipients either 1) receive anti-CMV prophylaxis, or 2) undergo regular monitoring for CMV reactivation with initiation of preemptive anti-CMV therapy if reactivation is detected. The only drugs currently approved for CMV prevention are ganciclovir and its prodrug, valganciclovir. Notably, neither of these drugs is approved specifically for CMV prophylaxis in HSCT recipients. As both drugs are associated with significant bone marrow toxicity, their use in the HSCT population is limited primarily to CMV preemptive therapy and to the treatment of CMV disease. Clearly, there is an unmet medical need for a safe and effective drug that could be administered for CMV prophylaxis in the HSCT population.

In the pivotal Phase 3 trial, P001, letermovir prophylaxis through Week 14 post-transplant was found to be highly effective at preventing clinically significant CMV infection through Week 24 post-transplant in HSCT recipients compared to placebo ($p<0.0001$). Clinically significant CMV infection was defined as either CMV viremia with resultant initiation of preemptive antiviral therapy or the development of CMV end-organ disease. CMV end-organ disease was uncommon, likely due to early treatment of CMV viremia, i.e., use of preemptive therapy; therefore, the primary endpoint was met primarily on the basis of preventing CMV viremia. In addition to reducing clinically significant CMV infection, letermovir use was associated with a statistically significant reduction in all-cause mortality at week 24.

There were several adverse events and laboratory abnormalities that were observed more frequently among subjects in the letermovir arm compared to the placebo arm: cardiac events, infections (excluding CMV infections), ear and labyrinth events, nausea, diarrhea, vomiting, abdominal pain, cough, headache, peripheral edema, fatigue, decreased platelet count, decreased hemoglobin, and increased serum creatinine. It is anticipated that many of these events will be included in the Adverse Reactions Section of the letermovir package insert. However, these events were largely non-serious in nature and are not felt to outweigh the clear and marked benefits of letermovir.

The other major safety consideration assessed in this review is the safety of the intravenous (IV) formulation of letermovir. In Trial P001, the IV formulation was given per investigators' discretion to subjects who were unable to take oral medications. In total, there were 99 subjects who received 1 or more doses of IV letermovir and the mean duration of exposure was 13.6 days. Review of safety events among subjects who received IV letermovir for 7 or more consecutive days did not identify any safety findings different from those observed in the overall population. However, given that 1) IV letermovir is associated with increased drug exposure compared to oral letermovir, and 2) the IV letermovir formulation contains hydroxypropyl-β-cyclodextrin which has been associated with nephrotoxicity in animals, additional safety data are of interest. As there is a need for an IV formulation of letermovir for use in the HSCT population and as there were no identified safety concerns among subjects who received IV letermovir in Trial P001, approval of IV letermovir with a PMR to obtain additional safety data is recommended.

In conclusion, approval of letermovir for the (b) (4) of CMV infection and/or disease in adult CMV-seropositive recipients of an allogeneic HSCT is fully supported by the available evidence of efficacy and safety. Based on the robust effect on a surrogate virologic endpoint (likely to predict clinical benefit), coupled with a reduction in all-cause mortality, this reviewer recommends letermovir for traditional approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cytomegalovirus (CMV) is a human herpes virus that infects 40-100% of adults worldwide. Like other herpes viruses, CMV establishes a latent infection that persists for life. • Symptomatic infection most commonly occurs in persons with impaired immunity. • Among allogeneic hematopoietic stem cell transplant (HSCT) recipients, CMV infection is a common complication. In these patients, CMV infection can cause CMV end-organ disease (e.g., pneumonitis, hepatitis) and has been associated with increased rates of GVHD and opportunistic infections. • Approximately 27,000 allogeneic HSCTs are performed each year. It is estimated that 65-80% of HSCT recipients are CMV seropositive and are therefore at high risk for CMV infection.	CMV is a highly prevalent human pathogen and is a significant source of morbidity and mortality in HSCT recipients.
Current Treatment Options	• There are two approaches to preventing CMV disease in transplant recipients: ○ Prophylaxis: transplant recipients receive antiviral therapy to prevent CMV infection and disease ○ Preemptive therapy: transplant recipients are monitored regularly for CMV infection and antiviral therapy is initiated if there is evidence of CMV replication in the blood. • Ganciclovir and valganciclovir are the only antiviral agents that are currently approved for CMV prevention in transplant recipients. They are associated with significant bone marrow toxicity and are not well-tolerated by HSCT recipients. Therefore, they are administered to HSCT recipients as preemptive therapy rather than prophylaxis. • Given the increase in mortality associated with CMV viremia as well as	There is a need for an effective and well-tolerated anti-CMV agent that could be administered to HSCT recipients prophylactically. A viable CMV prophylaxis option for HSCT recipients would not only help prevent CMV infection, but may improve overall transplant outcomes by preventing the indirect sequelae of CMV.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>the known indirect effects of CMV infection, it would be preferable to prevent rather than to treat CMV viremia.</td><td></td></tr>
<tr><td><u>Benefit</u></td><td>

The efficacy of letermovir was demonstrated in a single Phase 3 trial, P001, in which 373 CMV seropositive allogeneic HSCT recipients received letermovir.
The primary efficacy endpoint was clinically significant CMV infection at Week 24 post-transplant. This was defined as CMV viremia requiring preemptive CMV treatment or CMV end-organ disease. As shown in the table below, letermovir was associated with a highly significant reduction in clinically significant CMV infection at Week 24.

<table>
<tr><th>Efficacy Parameter</th><th>Letermovir N = 325</th><th>Placebo N = 170</th><th>Difference (95% CI), p-value</th></tr>
<tr><td>Overall Failures</td><td>122 (37.5%)</td><td>103 (60.6%)</td><td>-23.5 (-32.5, -14.6), <0.001</td></tr>
<tr><td>Clinically Significant CMV Infection</td><td>57 (17.5%)</td><td>71 (41.8%)</td><td>-</td></tr>
<tr><td>Initiation of PET</td><td>52 (16.0%)</td><td>68 (40.0%)</td><td>-</td></tr>
<tr><td>CMV End-Organ Disease</td><td>5 (1.5%)</td><td>3 (1.8%)</td><td>-</td></tr>
<tr><td>Discontinued from Study</td><td>56 (17.2%)</td><td>27 (15.9%)</td><td>-</td></tr>
<tr><td>Missing Outcome</td><td>9 (2.8%)</td><td>5 (2.9%)</td><td>-</td></tr>
</table>

Letermovir was also associated with a statistically significant reduction in all-cause mortality at Week 24 in Trial P001. No deaths in either arm appeared to be directly attributable to CMV infection. Thereby, the mechanism by which letermovir impacted mortality is incompletely understood and likely multifactorial.

</td><td>A large Phase 3 trial and a smaller Phase 2b trial demonstrated that letermovir is highly effective at preventing CMV infection in CMV seropositive HSCT recipients.

In trial P001, letermovir was also associated with a significant reduction in all-cause mortality at Week 24.

Given the close CMV monitoring with initiation of preemptive CMV therapy following detection of CMV viremia, CMV end-organ disease was very uncommon in both clinical trials.</td></tr>
</table>

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
• Despite the use of lower than recommended letermovir doses, the Phase 2b trial, P020, also demonstrated the efficacy of letermovir in the prevention of CMV infection in HSCT recipients. A dose-response was established in this trial, whereby all letermovir doses resulted in less CMV prophylaxis failure than placebo, and the two higher letermovir doses lead to a statistically significant reduction in prophylaxis failure.
<table>
<tr><th>Efficacy Parameter</th><th>Letermovir 60 mg/day N = 33</th><th>Letermovir 120 mg/day N = 31</th><th>Letermovir 240 mg/day N = 34</th><th>Placebo N = 33</th></tr>
<tr><td>Failure</td><td>16 (48.5%)</td><td>10 (32.3%)</td><td>10 (29.4%)</td><td>21 (63.6%)</td></tr>
<tr><td>CMV Prophylaxis Failure</td><td>7 (21.2%)</td><td>6 (19.4%)</td><td>2 (5.9%)</td><td>12 (36.4%)</td></tr>
<tr><td>Other Discontinuations</td><td>9 (27.3%)</td><td>4 (12.9%)</td><td>8 (23.5%)</td><td>9* (27.3%)</td></tr>
<tr><td>OR (95% CI)</td><td>0.5 (0.2, 1.6)</td><td>0.3 (0.1, 0.9)</td><td>0.2 (0.1, 0.7)</td><td>Reference</td></tr>
<tr><td>p-value</td><td>0.321</td><td>0.014</td><td>0.007</td><td>Reference</td></tr>
</table>
• To date, the efficacy of letermovir for the treatment of CMV infection and for the prevention of CMV infection outside of the HSCT population has not been studied.
</td><td></td></tr>
<tr><td><u>Risk</u></td><td>
• The overall safety database for letermovir comes primarily from Trial P001. Safety data from Trial P020 were also closely reviewed, but are less pertinent given the lower letermovir doses used in this trial.
• The most common adverse reactions (ARs) were nausea, diarrhea, and vomiting.
• There was a greater proportion of subjects in the letermovir arm than in the placebo arm that experienced cardiac events, ear and labyrinth
</td><td>The overall letermovir safety database is adequate, but the IV letermovir safety database is small.

There were no major safety signals identified that were unique to the IV formulation of letermovir. However, the limited number of</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	events, and infection events (excluding CMV infection). • The imbalance in cardiac events was driven largely by an increased incidence of tachyarrhythmias in the letermovir arm. Cardiac deaths were uncommon and balanced between the arms. • Laboratory results show that letermovir is associated with increased serum creatinine, decreased platelet count, and decreased hemoglobin. • The safety database for the IV formulation consists of 99 subjects who received one or more doses of IV letermovir and 72 subjects who received IV letermovir therapy for 7 or more consecutive days. • Letermovir drug exposure was approximately 3-fold higher following IV administration compared to oral administration in this population. Exposure-safety analyses revealed an association between the letermovir C_{max} and cardiac disorders, arrhythmias, and fluid overload. There were several limitations to these analyses that are discussed in the review. • The IV letermovir formulation contains hydroxypropyl betadex (hydroxypropyl-β-cyclodextrin) which has been associated with nephrotoxicity in animals and drug accumulation in humans with renal impairment. The increase in serum creatinine noted in Trial P001 was observed in subjects receiving either oral or IV letermovir; and thus the hydroxypropyl betadex may not be a concern.	subjects exposed to the IV formulation and the short duration of exposure should be conveyed in labeling. Although letermovir is associated with several adverse events and laboratory abnormalities, it was well-tolerated overall. Further, it appears to provide an improved toxicity profile over currently available anti-CMV therapies.
Risk Management	• The following events, classes of events, and laboratory abnormalities were more common among subjects receiving letermovir compared to those receiving placebo: nausea, diarrhea, vomiting, abdominal pain, cough, headache, peripheral edema, fatigue, cardiac events, ear and	The labeling proposed by the Applicant does not adequately convey the potential risks of letermovir to prescribers. In the package insert, inclusion of additional AEs and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	labyrinth events, infections, decreased platelet count, decreased hemoglobin, and increased serum creatinine. This reviewer recommends that these events be considered for inclusion in Section 6 of the letermovir package insert. • Presently, it is not anticipated that any of the safety findings will generate a Warning and Precautions statement in the label. • Additional safety data are needed for the IV formulation of letermovir. The best way to obtain this has not yet been determined. Current labeling should reflect the limited availability of safety data and should include a recommendation to switch to the oral formulation as soon as feasible. • Only a very small number of Black subjects were exposed to letermovir in Trials P001 and P020. We are therefore asking the Applicant to ensure that the planned renal transplant trial (P002) includes at least 20% black subjects to ensure that there are no differences in efficacy, safety, or PK in this population. Trial P002 will be conducted as a PMC.	laboratory abnormalities that occurred more frequently in letermovir subjects will be recommended. Labeling negotiations are ongoing at this time. Considering the higher rate of creatinine abnormalities among letermovir subjects receiving oral or IV letermovir, we anticipate including a recommendation to monitor renal function throughout the duration of letermovir use in the package insert. Given the limited available safety data for the IV letermovir formulation, the package insert will include a statement recommending that subjects be switched to oral therapy as soon as is feasible. Discussions are ongoing regarding how to best obtain additional safety data for the IV formulation. Additional safety data regarding letermovir use in Black subjects will be obtained in the planned Trial P002 in renal transplant recipients.

2 Therapeutic Context

2.1. Analysis of Condition

Cytomegalovirus (CMV) is a human herpes virus that infects 40-100% of adults worldwide. Primary infection in immunocompetent subjects is usually asymptomatic or may be associated with a self-limited mononucleosis-like syndrome and leads to a life-long CMV latency. Persons with compromised immunity are at increased risk for CMV reactivation. CMV reactivation among allogeneic hematopoietic stem cell transplant (HSCT) recipients is associated with significant morbidity and mortality. Among approximately 27,000 allogeneic HSCTs performed each year, it is estimated that 65-80% of recipients are CMV seropositive and are therefore at high risk for CMV infection. Among CMV seropositive allogeneic HSCT recipients, it has been reported that up to 80% will experience CMV infection in the absence of prophylaxis [1]. The most common manifestation of CMV infection is CMV viremia which may be associated with fever and laboratory abnormalities. CMV infection can also cause end-organ disease, potentially involving the gastrointestinal tract, liver, lungs, and other organ systems. CMV pneumonia is the most serious manifestation and has a mortality of up to 50% among HSCT recipients [1, 2]. In addition to these direct effects of CMV, the virus has also been associated with detrimental indirect effects such as increased rates of graft-versus host disease (GVHD), graft loss, opportunistic infections, and non-relapse mortality [1, 3].

2.2. Analysis of Current Treatment Options

There are two approaches to preventing CMV disease among transplant recipients. First, there is a prophylactic approach, whereby transplant recipients receive antiviral therapy to prevent CMV infection and disease. Second, there is a preemptive approach, whereby transplant recipients are monitored regularly for CMV infection (usually by CMV PCR testing of whole blood or plasma) and antiviral therapy is initiated in patients with evidence of CMV replication in the blood [1, 4].

Ganciclovir and its prodrug valganciclovir are nucleoside analogs that inhibit viral DNA polymerase and were originally approved in 1989 and 2001, respectively. They are the only antiviral agents that are currently FDA approved for CMV prevention in transplant recipients. These agents are associated with significant bone marrow toxicity and are not

well-tolerated by HSCT recipients. Therefore, a preemptive approach is more widely used among HSCT recipients; while prophylaxis is used more commonly in solid organ transplant (SOT) recipients. Without prophylaxis, it has been reported that as many as 80% of high-risk HSCT recipients will experience CMV reactivation and approximately 30% of these subjects will develop CMV end-organ disease [1]. Letermovir is intended to meet the need for a safe and effective CMV prophylactic agent for use in HSCT recipients. It acts by inhibiting the CMV viral terminase, an enzyme needed for cleavage of CMV DNA and packaging of cleaved CMV DNA into procapsids. Unlike the DNA polymerase targeted by ganciclovir and valganciclovir, the viral terminase does not have an analog in humans. Therefore, according to the Applicant, letermovir is not expected to exhibit the toxicities associated with agents currently available for CMV prevention. Additionally, as letermovir has a novel mechanism of action, cross-resistance between letermovir and currently available anti-CMV drugs is not anticipated.

Currently, there are no drugs approved specifically for CMV prophylaxis among HSCT recipients. FDA approved agents with anti-CMV activity include the previously described ganciclovir and valganciclovir, as well as foscarnet and cidofovir. See the table below for additional details regarding each of these currently available anti-CMV drugs. Intravenous (IV) ganciclovir was the first antiviral drug approved for the prevention of CMV disease in transplant patients (in HSCT and solid organ transplant recipients). The need for IV administration and the toxicity profile (primarily hematologic) of ganciclovir have limited its use for prophylaxis against CMV in transplant patients. Oral ganciclovir was later developed and is approved for the prevention (prophylaxis) of CMV disease in solid organ transplant patients. However, this formulation has poor bioavailability and prophylaxis requires that patients take four capsules three times daily, thus making compliance challenging. Subsequently, valganciclovir, a more orally bioavailable form of ganciclovir, was approved for CMV prophylaxis in solid organ transplant recipients. Valganciclovir replaced oral ganciclovir use and oral ganciclovir is not currently available in the United States.

Valganciclovir and ganciclovir may be used off-label for CMV prophylaxis among HSCT recipients. However, due to the significant myelosuppression and the resultant increase in the incidence of opportunistic infections associated with the use of these agents in HSCT recipients, this practice is uncommon. Foscarnet and cidofovir are approved for the treatment of CMV retinitis in HIV patients. They are also used off-label for the treatment of CMV infections in transplant patients [5]. However, because of greater toxicities relative to other anti-CMV agents (most notably severe renal toxicity and severe electrolyte

abnormalities), their role in treating CMV infections in transplant patients has been limited to patients who are failing ganciclovir/valganciclovir treatment [5].

Table 1. Summary of Currently Approved CMV Therapies

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Agents for CMV Prevention and Treatment						
Ganciclovir-IV (GCV)	Treatment of CMV retinitis in immunocompromised patients Prevention of CMV disease in transplant recipients	1989	Retinitis Treatment and Disease Prevention: Induction: 5 mg/kg IV every 12 hours Maintenance: 5 mg/kg IV daily	Reduction of CMV disease through 120 days post-transplant (16% vs 43% ($p < 0.001$) in GCV and placebo arms, respectively) when administered prophylactically to heart transplant recipients Reduction in CMV disease through 100 days post-transplant (3% vs 43% ($P < 0.001$) in GCV and placebo arms, respectively) when administered preemptively to HSCT recipients	Bone marrow suppression, potential testicular/fetal toxicity, and carcinogenicity	There is also an oral GCV formulation but it is not currently available in the US
Valganciclovir (VGCV)	Treatment of CMV retinitis in patients with AIDS Prevention of CMV disease in SOT recipients	2001	Retinitis Treatment: Induction: 900 mg PO twice daily Maintenance: 900 mg PO daily Disease Prevention: 900 mg PO once daily	VGCV was non-inferior to oral GCV for the prevention of CMV disease in the first 6 months after SOT (12% vs 15% (95% CI -0.042, 0.110) ($p = 0.38$)) in the VGCV and GCV arms, respectively	Bone marrow suppression, potential testicular/fetal toxicity, and carcinogenicity	Recommended duration of prophylaxis is 100 days in heart and kidney-pancreas recipients and 200 days in kidney recipients. Not approved for CMV prevention in liver transplant recipients.
FDA Approved Agents for CMV Treatment Only						

Foscarnet (FOS)	Treatment of CMV retinitis in patients with AIDS	1991	Induction: 60 mg/kg IV every 8 hours or 90 mg/kg every 12 hours Maintenance: 90 to 120 mg/kg daily	Progression of CMV retinitis was significantly delayed by FOS compared to placebo (median time to progression was 93 days with FOS and 22 days with placebo). Compared to GCV, median time to progression of retinitis was similar with FOS (59 days for FOS and 56 days for GCV).	Renal impairment, electrolyte abnormalities, bone marrow suppression, seizures, hypersensitivity reactions, QT prolongation	Used off-label for the treatment of CMV infection in transplant recipients in cases of resistant/ refractory infection or intolerance of other treatment options. Toxicity precludes use for prophylaxis.
Cidofovir (CDV)	Treatment of CMV retinitis in patients with AIDS	1996	Induction: 5 mg/kg IV weekly Maintenance: 5 mg/kg IV every 2 weeks	In a trial of delayed vs. immediate treatment of CMV retinitis with CDV, immediate CDV therapy was associated with a significantly prolonged median time to retinitis progression (120 days and 22 days for immediate and delayed groups, respectively).	Renal impairment, neutropenia, and potential carcinogenicity	Used off-label for the treatment of CMV infection in transplant recipients in cases of resistant/ refractory infection or intolerance of other treatment options. Toxicity precludes use for prophylaxis.

Source: FDA labels

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Letermovir is an NME that is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The initial IND for oral letermovir (104706) for the prevention of human CMV disease was opened by AiCuris GmbH & Co. KG on February 18, 2009. After a 30-day safety review, it was determined the Sponsor may proceed with the proposed clinical investigation on March 20,

2009. Subsequently, on April 9, 2013, sponsorship of IND 104706 was transferred from AiCuris to Merck Sharpe & Dohme Corp. An IND for intravenous letermovir (118361) was opened by Merck on August 22, 2013. This section describes key events and activities that occurred under these INDs during the letermovir clinical development program.

Fast Track Designation
On May 25, 2011, FDA granted Fast Track designation to letermovir for the prevention of human CMV disease in transplant recipients.

Orphan Drug Designation
On December 12, 2011, FDA approved the request for Orphan drug designation for letermovir for the prevention of human CMV viremia and disease in at risk populations.

Type C Meeting
On February 7, 2012 a face-to-face Type C meeting with AiCuris was conducted. Preliminary data from the Phase 2b Trial P020 were presented and preliminary Phase 3 plans were discussed. Important clinical considerations discussed at this meeting included the following:

- DAVP agreed that a large single Phase 3 trial supported by the Phase 2b trial would be acceptable for an NDA if the results were robust. A safety database of 300 to 500 patients was recommended.
- DAVP recommended the use of a clinical endpoint for the pivotal Phase 3 trial, and should AiCuris choose to use a virologic endpoint for their Phase 3 trial, the application would be considered for accelerated approval.
- (b) (4)

End-of-Phase 2 Meeting
A face-to-face meeting was held with Merck on September 25, 2013. The major clinical considerations discussed at this meeting are summarized below.

- The general study design of the pivotal Phase 3 trial in HSCT recipients was agreed upon.
- Merck proposed a CMV DNA threshold for the initiation of preemptive therapy of 150 copies/mL in high risk subjects and 300 copies/mL in low risk subjects. DAVP requested that a threshold of 1000 copies/mL be used for low risk subjects. Merck explained that this threshold was chosen based on recommendations from expert consultants. DAVP ultimately agreed with Merck's choice of viral load thresholds for preemptive therapy initiation.

- DAVP expressed concerns regarding the high anticipated discontinuation rate (20%), and recommended that the sponsor follow discontinued patients as much as possible.
- DAVP agreed with Merck's plan to monitor serum hormone levels in Phase 3 studies. However, Merck was informed that the Division may ask for a post-marketing commitment or requirement to further investigate whether letermovir significantly affects spermatogenesis (including semen analysis and hormone monitoring) in adult male transplant recipients.
- DAVP reiterated its stance regarding the acceptability of a single, robust Phase 3 trial and again informed Merck that an application based on a virologic endpoint would be considered for accelerated, not traditional, approval.
- DAVP stated that they would like to have at least 300 subjects exposed to letermovir for at least 100 days at the proposed dose and duration. Regarding the IV letermovir safety database, the FDA stated that whether there would be sufficient safety data at the time of NDA submission would be a review issue.
- The general study design for a CMV prophylaxis trial in renal transplant recipients was agreed upon. However, DAVP informed Merck that this trial would not provide sufficient evidence for a broad SOT indication.

Pre-NDA Meeting

On December 14, 2016 a face-to-face meeting was conducted with Merck. Preliminary data from Trial P001 were presented. The major clinical discussions from this meeting are summarized below.

- DAVP recommended that Merck apply for Breakthrough Therapy designation.
- Although letermovir has orphan designation and PREA requirements do not apply,
  (b) (4)
- Merck proposed the provision of a clinical study report (CSR) including Week 48 efficacy and safety data in lieu of the safety update report (SUR) for the pending NDA applications. DAVP agreed with this plan.
- DAVP informed Merck that based on the observed reduction in all-cause mortality in trial P001, the letermovir NDAs may be considered for traditional approval.
- Merck confirmed their intention to complete a trial in renal transplant recipients whether or not it is needed as a confirmatory trial.

Breakthrough Therapy Designation

On February 27, 2017, Breakthrough therapy designation was granted for IV and oral letermovir for the prevention of CMV infection and/or disease in adult CMV-seropositive recipients [R+] of allogeneic HSCT.

Additional details of the milestone meetings can be found in the official meeting minutes archived in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). All previous reviews can also be accessed in DARRTS for additional information.

3.3. Foreign Regulatory Actions and Marketing History

Letermovir is not currently marketed in any country. However, an application for letermovir was pending in the European Union (EU) at the time of this review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspection sites were selected from the pivotal Phase 3 trial, P001. Five sites were selected, 2 US sites and 3 international sites. These sites were chosen based on enrollment, protocol violations, and previous inspection history. Of note, two of these sites also participated in the Phase 2b trial, P020, though records from the Phase 2b trial were not examined as part of the inspection.

Preliminary reports from OSI suggested that there were no problems identified at any of the inspected sites. However, the final reports from the clinical site inspections were pending at the time of this review.

4.2. Product Quality

Letermovir is supplied as an immediate-release, film-coated tablet or as a liquid (b) (4) for intravenous administration.

- Tablet:

The letermovir tablet comes in two strengths, 240 mg and 480 mg. The letermovir drug substance is an amorphous form that is slightly hygroscopic. It is known to be stable for at least (b) (4) months at (b) (4) relative humidity. The tablets include the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone 25, colloidal silicon dioxide, magnesium stearate, (b) (4) Carnauba Wax, (b) (4) film coating contains lactose monohydrate, hypromellose 2910, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (480 mg tablet only). The formulation for the commercial batches is the same as the formulation for the batches used in the Phase 3 clinical trial.

- Injection:
  The injectable letermovir formulation comes as a 20 mg/ml sterile (b) (4) solution in 240 mg/vial or 480 mg/vial. It is administered as an IV infusion at a constant rate over approximately 60 minutes after diluting with either normal saline or 5% dextrose. Hydroxypropyl β-cyclodextrin is used (b) (4) and the 240 mg and 480 mg letermovir doses contain 1800 mg and 3600 mg of hydroxypropyl β-cyclodextrin, respectively. Additional components of the injectable formulation are sodium hydroxide (b) (4), sodium chloride (b) (4) and water for injection.

Reviewer Comment: The use of hydroxypropyl β-cyclodextrin (b) (4) is of particular interest as it has been associated with nephrotoxicity in animal studies and has been shown to accumulate in humans with renal impairment. The amount of hydroxypropyl β-cyclodextrin contained in both letermovir doses does not exceed the amount of hydroxypropyl β-cyclodextrin contained in previously approved drugs. Further, it is less than the maximum daily parenteral dose recommended by the EMA (250 mg/kg/day for persons older than 2 years of age)(http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177936.pdf). However, it should be noted that the maximum daily dose determined by the EMA is based on a maximum duration of exposure of 21 days.

4.3. Clinical Microbiology

This section provides a brief summary of key letermovir nonclinical virology characteristics. Discussions regarding clinical virology assessments pertaining to the pivotal clinical trials are found in Section 6. Please see the Clinical Virology Review of Dr. Takashi Komatsu for additional details.

CMV is a large, linear double-stranded DNA virus that belongs to the Herpesviridae family.

Letermovir targets the CMV terminase complex, which is necessary for the generation of unit length DNA genomes. In cell culture assays, the median EC_{50} value of letermovir was 1.9 nM (range 0.1 nM-5.8 nM, n = 29), 2.0 nM (range 0.7 nM-6.1 nM, n = 27), 2.3 nM (range 1.5 nM-3.4 nM, n = 11), and 2.9 nM (range 2.6 nM-3.2 nM, n = 3) against human CMV gB genotypes 1, 2, 3, and 4, respectively. The combination of letermovir with other antiviral agents with anti-CMV activity (e.g., ganciclovir, foscarnet) did not demonstrate antagonism. In cell culture, the following substitutions were observed on the pUL56 (L51M, V231A/L, V236L/M, E237D, L241P, T244K/R, L257I, F261C/L/S, Y321C, C325F/R/Y, M329T, and R369G/M/S) and pUL89 (A345S) components of the CMV terminase complex. These substitutions were all associated with at least a two-fold reduction in susceptibility to letermovir, but no cross resistance to other antivirals was detected. Of note, the pUL56 mutants all displayed fitness comparable to that of wildtype virus.

In the clinical trial P001, resistance-associated substitutions identified in cell culture were detected in 37.4% of letermovir subjects with on-treatment virologic failure and available genotypic data. Please see Section 6.1.2 for additional details regarding the emergence of resistance in Trial P001.

4.4. Nonclinical Pharmacology/Toxicology

This section provides a brief overview of the key findings from nonclinical toxicology studies conducted in support of this application. Please refer to the Pharmacology/Toxicology Review by Dr. David McMillan for additional details.

Safety Pharmacology and Repeat-Dose Toxicology

Safety pharmacology studies **(**cardiovascular, respiratory, neurological, renal and gastrointestinal) were performed in rats and dogs. GLP repeat-dose toxicology studies were performed in mice, rats, and monkeys for durations of up to 13, 26, and 39 weeks, respectively. Repeat-dose studies in rats revealed the liver and testes to be target organs of toxicity. Specifically, increased vacuolization of the testes and increased liver weight, increased centrilobular fat deposition in the liver, and increased liver function tests (LFTs) were observed in rats. Exposure multiples at the NOAELs in rats were 2.7-, 1.6-, and 10.8-fold in the 4-, 13-, and 26-week oral studies, respectively, and 1.3-fold in the 4-week IV study, relative to the proposed clinical dose. In the oral repeat-dose studies in monkeys, adverse kidney effects, reduced health status, and decreased body weight were observed, and several animals were euthanized *in extremis* after receiving doses exceeding the maximum tolerated dose. The cause of death in the euthanized animals was either undetermined or attributed to renal insufficiency. Exposure multiples at the NOAELs in monkeys were 0.3-, 1.0-, and 0.8-fold in the 4-, 13-, and 39-week oral studies, respectively, and 1.0-fold in the 4-week IV study, relative to the proposed clinical dose. Lastly, adverse IV vehicle effects due to hydroxypropyl β-cyclodextrin were observed in the kidney in all animals, including controls, in the repeat-dose IV rat studies.

Fertility and Early Embryonic Development

- Female fertility: No toxicities were observed in rat fertility studies up to the highest dose tested.
- Male fertility: Severe testicular toxicities were observed in the rat fertility studies, similar to those observed in the repeat-dose study in rats. Exposure multiples at the male NOAEL in the rat fertility study were 0.5-fold. No adverse effects were seen in a 13-week fertility study in male monkeys up to the highest dose tested. In addition, testicular toxicity was not observed in a 13-week general toxicity study in mice, though this study was not designed to assess testicular toxicity.
- Embryo-fetal development: Both maternal and fetal toxicities were observed in the embryo-fetal development studies in rats and rabbits, including euthanasia *in extremis*, spontaneous abortions, adverse clinical signs (reddish vaginal discharge, cold to touch, etc.), decreased maternal and fetal weights, decreased food consumption, umbilical cord shortening, and fetal skeletal deviations and malformations. Exposure multiples at the maternal and fetal NOAELs are 0.3- and 4.3-fold in rats, and 0.8-fold for both in rabbits, relative to the proposed clinical dose.
- Pre-/post-natal development: A study in rats showed total litter loss in five parent animals, decreased weight gain, and slight delays in pinna unfolding, visual placing of forepaws, and vaginal opening in pups. Exposure multiples at the fetal/neonatal NOAELs are 1.5-fold relative to the proposed clinical dose.

Phototoxicity/Local Tolerance

Letermovir was not associated with phototoxicity or skin irritation. However, a slight local intolerance occurred when letermovir was administered intravenously, intra-arterially, and intramuscularly.

Genetic Toxicology

Genotoxicity studies were negative and carcinogenicity studies were not performed given the intended treatment duration of less than 6 months.

4.5. Clinical Pharmacology

This section summarizes the key outcomes of the clinical pharmacology discipline review, including highlights of pharmacokinetics (PK) and pharmacodynamics (PD), and dose-response relationships that support dose selection. Please see the Clinical Pharmacology review by Dr. Mario Sampson for full details.

4.5.1. Mechanism of Action

Letermovir is a CMV viral terminase inhibitor

4.5.2. **Pharmacodynamics**

In the Phase 2b trial, P020, letermovir doses of 60 mg, 120 mg, and 240 mg daily were evaluated in HSCT recipients. These doses were chosen based on data from healthy subjects showing that 60 mg of letermovir would result in an unbound plasma concentration exceeding the EC_{90} (effective concentration at which virus replication is inhibited by 90 percent) threshold for greater than 12 hours and that 120 mg and 240 mg of letermovir would result in unbound plasma concentration/EC_{90} ratios > 1 throughout the dosing interval.

In P020, all three doses were found to be associated with a decreased risk of CMV prophylaxis failure compared to placebo. The rate of efficacy increased with ascending letermovir doses [see Section 6.2.2]. The pharmacokinetic (PK) and pharmacodynamic (PD) data derived from P020 were used to derive the proposed letermovir dose of 480 mg daily, reduced to 240 mg daily if given with cyclosporine. Specifically, it was determined that an area under the plasma concentration versus time curve at steady state levels ($AUCss,\tau$) < 45,000 ng.h/mL was associated with an increased rate of CMV prophylaxis failure. Simulations from the population PK analysis indicated that an $AUCss,\tau \geq 45,000$ ng.h/mL could be achieved in >90% of the population with a letermovir dose of 480 mg daily. A letermovir dose of 240 mg daily when given concomitantly with cyclosporine was predicted to result in drug exposures similar to 480 mg of letermovir alone. This dose was then studied in the pivotal Phase 3 trial, P001. The findings of P001 provide confirmation that the proposed dose is both efficacious and reasonably well-tolerated.

4.5.3. **Pharmacokinetics**

Absorption, Distribution, Metabolism, and Elimination

Based on population PK analyses, the absolute bioavailability of letermovir in patients and healthy adults were estimated to be 94% and 35%, respectively. Letermovir reaches maximum plasma concentration 0.75 – 2.25 hours after oral administration. Letermovir can be taken with or without food.

Letermovir is highly protein bound (approximately 99%) in vitro. Hepatic uptake is mediated by OATP1B1/3.

Metabolism is a minor elimination pathway for letermovir. The drug is predominately eliminated in feces as unchanged parent drug. Urinary excretion is 2% of the letermovir dose. Steady-state levels are reached in 9-10 days. After a 480 mg IV dose in healthy adults, the mean terminal half-life is approximately 12 hours.

Hepatic Impairment

The hepatic impairment study was performed using a 60 mg dose of letermovir, which is substantially lower than the recommended clinical dose. In this study, letermovir was observed to be primarily hepatically eliminated. Unbound drug exposures increased approximately 2 fold in subjects with moderate hepatic impairment and approximately 5 fold in subjects with severe hepatic impairment. The effect of mild hepatic impairment on drug exposure was not evaluated. Because the letermovir dose used in the hepatic impairment study was lower than the recommended dose, there are insufficient data to recommend dosing for patients with hepatic impairment. Discussions regarding the use of letermovir in patients with mild, moderate, and severe hepatic impairment are ongoing at the time of this review. It is anticipated that a hepatic impairment study using the proposed clinical dose of 480 mg will be requested as a postmarketing requirement (PMR) or a postmarketing commitment (PMC).

Renal Impairment

The renal impairment study was performed using a 120 mg dose of letermovir, which is substantially lower than the recommended clinical dose. Despite only a small fraction of letermovir being excreted renally, unbound drug exposures were increased approximately 2 fold in subjects with moderate and severe renal impairment. Because the letermovir dose used in the renal impairment study was lower than the recommended dose, there are insufficient data to recommend dosing for patients with renal impairment. A renal impairment study using the proposed clinical dose of 480 mg may be requested as a PMR or PMC.

Gender, Age, and Race

In Phase 1 studies, it was noted that there was an increase in drug exposure of 50-150% among Japanese subjects. However, among a small subset of Asian subjects in the Phase 3 Trial, P001, there was less than a 50% increase in drug exposure which is not thought to be clinically meaningful. There were no other notable differences in drug exposure among demographic subgroups.

HSCT Recipients

Following oral administration, HSCT recipients have a lower C_{max} and AUC compared to those in healthy adults. Following intravenous administration, HSCT recipients have a similar AUC and a lower C_{max} compared to those in healthy adults.

Drug Interactions

Summary of the effect of letermovir on other drugs:

- Letermovir is an inhibitor of CYP3A, CYP2C8, BCRP, BSEP, MRP2, OATP1B1/3, and OAT3
- Letermovir is an inducer of CYP2B6 and CYP3A

Summary of the effect of other drugs on letermovir:

- Letermovir is a substrate of UGT1A1/3, CYP3A, CYP2D6, CYP2J2, OATP1B1/3, and Pgp

Key drug-drug interactions:

- Interaction between letermovir (an OATP1B1 substrate) and the commonly used immunosuppressant, cyclosporine (an OATP1B1 inhibitor): In a phase 1 study, cyclosporine was shown to increase the AUC of oral letermovir approximately 2 fold. Therefore, in Trial P001, the letermovir dose was reduced from 480 mg daily to 240 mg daily when given with cyclosporine. The effect of cyclosporine and letermovir dose/route of administration on the letermovir AUC in Trial P001 is shown in the table below. Although the AUC varies by route of administration and the use of cyclosporine, the exposure-efficacy relationships were flat. Therefore, according to the Clinical Pharmacology review, the proposal to reduce the standard letermovir dose of 480 mg daily to 240 mg daily in the setting of cyclosporine coadministration is considered acceptable for both the oral and IV formulation.

Table 2. P001: Letermovir AUC (ng*h/mL) Values by Dose and Route of Administration

N	Letermovir dose (mg)	Letermovir route of administration	Use of cyclosporine	Median AUC (90% prediction interval)
139	480	PO	No	34400 (16900, 73700)
10	480	IV	No	100000 (65300, 148000)
139	240	PO	Yes	60800 (28700, 122000)
5	240	IV	Yes	70300 (46200, 106000)

Source: Exposure-response dataset (N) and proposed labeling (AUC values).

- Interaction between the antifungal agent voriconazole, and letermovir: In a drug interaction study in which voriconazole and letermovir were coadministered, the voriconazole AUC ratio was found to be 0.56 (90% CI: 0.51, 0.62). Due to the significant reduction in voriconazole exposure when given concomitantly with letermovir, use of voriconazole with letermovir is not recommended.

  Reviewer Comment: In Trial P001, investigators were made aware of the potential interaction between letermovir and voriconazole. Use of an antifungal other than voriconazole was recommended. In cases where coadministration of voriconazole and letermovir was deemed necessary, close monitoring for breakthrough fungal infections was recommended. Ultimately, 28.4% of letermovir subjects and 28.1% of placebo

subjects received voriconazole during the treatment period of P001. Pooling of fungal PTs showed that 1.6% of letermovir subjects and 1.0% of placebo subjects experienced a serious, on-treatment fungal AE). Although the frequency of serious fungal infections was slightly higher in the letermovir arm, whether this is due to chance or some other factor is not known. Given the known drug-drug interaction, voriconazole levels should be closely monitored if voriconazole and letermovir must be coadministered (despite the recommendation not to) in clinical practice.

- CYP2C8: Completed studies and modeling have not determined if letermovir induces CYP2C8. A postmarketing in vitro study evaluating induction of CYP2C8 by letermovir will likely be requested.

- Drug interactions with IV letermovir: All drug interaction studies were conducted using oral letermovir. These data will likely be extrapolated to IV letermovir.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable to this application.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below contains a summary of the Phase 2 and Phase 3 trials in the Applicant's clinical safety database for letermovir that were submitted with this NDA.

Table 3. Controlled Studies to Support the Efficacy and Safety of Letermovir

Trial Identity/ Phase	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
P001 Phase 3	Double-blind, randomized, placebo-controlled trial	480 mg PO or IV daily (reduced to 240 mg if on concomitant CsA); OR Placebo PO or IV daily	Clinically significant CMV infection (initiation of PET or CMV end-organ disease) at Week 24 post-transplant	Subjects were treated through Week 14 and followed through Week 48 post-transplant	570 (376 letermovir and 194 PBO)	CMV R+ HSCT recipients	67 sites, 20 countries
P020 Phase 2b	Double-blind, randomized, placebo-controlled trial	Letermovir 60 mg, 120 mg, or 240 mg PO daily; OR Placebo daily	CMV prophylaxis failure (CMV viremia leading to pre-emptive treatment or CMV disease) at Week 12 post-transplant	Subjects were treated through Week 12 post-transplant, then followed for an addition 7 days	100 (67 letermovir and 33 PBO)	CMV R+ HSCT recipients	23 sites, 2 countries (Germany and US)

Abbreviations: CsA, cyclosporine; HSCT, hematopoietic stem cell transplant; PBO, placebo; PET, pre-emptive therapy; R+, recipient CMV seropositive.

5.2. Review Strategy

This clinical review reflects extensive collaboration with the statistical reviewer, Dr. Fraser Smith, and the clinical virology reviewer, Dr. Takashi Komatsu. In addition, there were significant interactions with the clinical pharmacology, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. The assessments of the other reviewers are summarized in this document in the relevant sections. Complete descriptions of their findings are available in their respective discipline reviews.

In addition to the aforementioned interdisciplinary collaboration, there was also collaboration with clinical reviewers from the Division of Cardiovascular and Renal Products and the Division of Bone, Reproductive, and Urologic Products. Consultation provided by these clinical reviewers was integral to our assessment of potential safety signals identified in this application.

The JumpStart program offered by the Computational Science Center (CSC) at the Center for Drug Evaluation and Research (CDER) was utilized for this review. The JumpStart analysts assessed data fitness and provided exploratory safety analyses. In addition, several other JumpStart pilot programs were utilized in the course of this review. The Demographic Service helped explore safety findings among specific demographic sub-populations. The Clinical Investigator Site Selection Tool and the JMP Clinical Anomaly Detection program were used to help identify clinical sites for inspection.

The clinical review for letermovir is based primarily on the Phase 3 trial, P001, and the Phase 2b trial, P020. Only Trial P001 studied the to-be-marketed dose and duration of letermovir, therefore findings from this trial are emphasized throughout this review. Trial P020 studied doses lower than the to-be-marketed letermovir dose. Nonetheless, this study also demonstrated the efficacy of letermovir in CMV prevention in HSCT recipients. It also provides additional safety data and provides an opportunity to assess for dose-related safety findings.

6 Review of Relevant Individual Trials Used to Support Efficacy

The Applicant states that clinical trials conducted to support the licensure of letermovir were all conducted following Good Clinical Practice standards and considerations for the ethical treatment of human subjects.

6.1. Trial P001

6.1.1. Study Design

Overview and Objective

This was a Phase 3, multicenter, randomized, placebo-controlled, double-blind study of letermovir for the prevention of clinically significant CMV infection in adult CMV seropositive allogeneic HSCT recipients. The primary objective of Trial P001 was to evaluate the efficacy of MK-8228 in the prevention of clinically significant CMV infection through Week 24 post-transplant following administration of letermovir or placebo.

Trial Design

Following transplantation, eligible subjects were randomized in a 2:1 ratio to receive either letermovir or placebo. Study drugs were initiated any time from the time of transplantation until 28 days post-transplantation. Each subject received the assigned drug through Week 14 post-transplant. The primary efficacy endpoint was assessed at 24 weeks post-transplant. Subjects were then followed through 48 weeks post-transplant. The dose of letermovir was 240 mg once daily for subjects who received concomitant cyclosporine and 480 mg once daily for subjects not on cyclosporine. Both the oral (tablet) and IV formulation of letermovir (and placebo) were available for therapy. The IV formulation was administered when subjects were not able to take oral therapy or when there was a concern for malabsorption. The use of the IV formulation was generally limited to 4 weeks or less in duration. However, ongoing IV administration beyond 4 weeks was permitted if the investigator felt that the benefit/risk ratio supported continued administration.

Study Endpoints

<u>Primary Endpoint:</u>

Proportion of subjects with clinically significant CMV infection through Week 24 post-transplant, defined as the occurrence of either one of the following outcomes:

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

Initiation of preemptive therapy (PET) in this study refers to the practice of initiating therapy with an approved anti-CMV agent when active CMV viral replication is documented. Determination of CMV end-organ disease was based on definitions by Ljungman et al. and confirmed by an independent, blinded Clinical Adjudication Committee [6]. The viral load thresholds for initiation of preemptive treatment in this trial were based on risk factor for reactivation of CMV disease and were as follows:

- During the study treatment period (through Week 14 post-transplant)
    - High risk: viral DNA ≥150 copies/mL
    - Low risk: viral DNA >300 copies/mL

- After Week 14 post-transplant
    - High risk: viral DNA >300 copies/mL
    - Low risk: viral DNA >300 copies/mL

Secondary Endpoints:

- Proportion of subjects with clinically significant CMV infection through Week 14 post-transplant
- Time to onset of clinically significant CMV infection through Week 24 post-transplant
- Proportion of subjects with CMV disease through Week 14 post-transplant and Week 24 post-transplant
- Proportion of subjects with initiation of PET for documented CMV viremia through Week 14 post-transplant and Week 24 post-transplant
- The time to initiation of PET for documented CMV viremia through Week 24 post-transplant.

Exploratory Endpoints:

- Proportion of subjects with CMV disease through Week 48 post-transplant
- Proportion of subjects with all-cause mortality through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant
- Proportion of subjects with opportunistic infection (i.e., systemic bacterial infection or invasive fungal infection) through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant
- Proportion of subjects with GVHD through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant
- Proportion of subjects with all re-hospitalizations and re-hospitalizations for CMV infection/disease through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant.
- Proportion of subjects with documented viremia (as measured by the central laboratory) through Week 14 post-transplant and Week 24 post-transplant.
- Proportion of subjects with engraftment through Week 14 post-transplant and Week 24 post-transplant

Statistical Analysis Plan

The primary hypothesis was that letermovir is superior to placebo in the prevention of clinically significant CMV infection. The Mantel-Haenszel method was used to compare the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant between the letermovir and placebo arms. A 1-sided p-value ≤ 0.0249 was needed to conclude that letermovir was superior to placebo. The primary efficacy analysis was performed on the Full Analysis Set (FAS) population, which for Trial P001 included all subjects who had received at least one dose of study drug and had a negative CMV DNA on Day 1 of study drug

administration. The missing data were handled using the Non-Completer = Failure approach.

Safety assessments included AE reports, laboratory tests, vital signs and ECG measurements. The Applicant used the 3-tiered approach for safety signal detection in this trial. According to this approach, Tier 1 events were events for which there was a pre-specified hypothesis regarding a potential increase or decrease in frequency of the event in association with the drug of interest. There were no Tier-1 events for this trial. Tier 2 events were events that are common, but not pre-specified. For this study, Tier 2 events were defined as AEs that occurred in 4 or more subjects in at least 1 treatment group. In addition, the following were also analyzed as Tier 2 events: the proportion of subjects with (1) at least one AE; (2) a drug related AE; (3) an SAE; (4) a serious and drug-related AE and (5) an AE leading to discontinuation. Assessment of Tier 2 AEs included calculations of point estimates for each treatment group and point estimates with 95% confidence intervals for between arm comparisons. These confidence intervals were not adjusted for multiplicity and were only intended to identify potentially meaningful differences between arms. Tier 3 events are uncommon events (< 4 subjects in both treatment groups) and include any events not included as Tier 2 events. The safety analyses were conducted using the all subjects as treated (ASaT) population. This population included all subjects who had received at least one dose of study drug.

Please see the Biometrics review by Dr. Fraser Smith for additional details regarding the statistical analysis plan.

Protocol Amendments

There were three protocol amendments for Trial P001.

- **Amendment 1.** This amendment included the following notable changes:
    - The collection of plasma for testing for CMV viremia, creatinine clearance, and liver function testing was changed from 7 days to 5 days prior to randomization (per Agency request).
    - Guidance regarding viral load threshold for the initiation of PET was revised to include different parameters for viremia occurring during the study period vs viremia occurring after Week 14 (per Agency request). The viral load thresholds described in the text above reflect these changes.
- **Amendment 2**. This amendment included the following notable changes:
    - Asian descent was added as an exclusion criterion.
    - The protocol was changed to allow a subject to reinitiate study drug if the confirmatory central laboratory test result for CMV DNA PCR, obtained on the day of PET initiation, was negative and PET was stopped.
- **Amendment 3.** This amendment included the following notable changes:
    - The 480 mg oral tablet formulation was incorporated into the protocol (prior protocols involved the use of two 240 mg tablets).

- The Asian descent exclusion criterion was removed. This change was based on data from Trial P032 that suggested that letermovir could be administered to Japanese subjects at the doses specified in Trial P001 without posing significant risk.

In addition to the significant protocol changes described above, each amendment included several minor changes that were not felt to impact the overall conduction of the trial.

6.1.2. Study Results

Patient Disposition

A total of 738 subjects provided informed consent and were screened for study eligibility. Of these, 570 subjects were randomized. Among the 168 subjects who were screened but not randomized, the majority (161) were screen failures. The most common reasons for screen failure were evidence of CMV viremia from time of signing of the informed consent form (ICF) or from time of transplantation, receipt of anti-CMV therapy within 7 days prior to screening, and determination that recipient was CMV seronegative. In addition to the screen failures, there was one adverse event, one death, and 5 withdrawals of consent by subject prior to randomization. At the time of database lock for the original NDA submission, just over 10% of subjects in each arm were ongoing in the study (had reached Week 24 and were in the secondary follow-up period). The treatment and study disposition of the randomized subjects at the time of database lock is presented in the table below.

Table 4. P001: Subject Disposition

Subject Disposition	Letermovir	Placebo
Subjects randomized	376	194
Subjects enrolled and treated with at least one dose of study drug (ASaT population)	373	192
Subjects enrolled, treated with at least one dose of study drug, and with a negative CMV DNA on Day 1 (FAS population)	325	170
Treatment disposition*		
Completed treatment	267/373 (71.6%)	80/192 (41.7%)
Discontinued treatment	106/373 (28.4%)	112/192 (58.3%)
Lack of efficacy	24 /373 (6.4%)	82/192 (42.7%)
Excluded medication**	3/373 (0.8%)	0/192 (0.0%)
Subject non-compliant	5/373 (1.3%)	1/192 (0.5%)
Withdrawal by subject	20/373 (5.4%)	4/192 (2.1%)
Adverse event	42/373 (11.3%)	19/192 (9.9%)
Death	5/373 (1.3%)	4/192 (2.1%)
Study disposition		
Subject ongoing at database lock	44/373 (11.8%)	20/192 (10.4%)
Completed study (through week 48)	202/373 (54.2%)	100/192 (52.1%)
Discontinued study	127/373 (34.0%)	72/192 (37.5%)
Physician decision	15/373 (4.0%)	5/192 (2.6%)
Lost to follow-up	8/373 (2.1%)	4/192 (2.1%)
Subject non-compliant	1/373 (0.3%)	0/192 (0.0%)
Withdrawal by subject	28/373 (7.5%)	17/192 (8.9%)
Adverse event	6/373 (1.6%)	3/192 (1.6%)
Death	69/373 (18.5%)	43/192 (22.4%)

Source: ADSL and DS datasets
*Treatment discontinuation categories are mutually exclusive.
**Subject required initiation of a prohibited medication

The most pronounced difference in disposition events between the two arms was the higher rate of treatment discontinuation due to lack of efficacy in the placebo arm. These discontinuations represent subjects who experienced CMV reactivation and started PET. Also of note, more letermovir subjects stopped treatment due to withdrawal by subject and more placebo subjects discontinued the study prematurely due to death.

Week 48 CSR

The 48 Week CSR submitted by the Applicant in the middle of the review cycle contained the disposition of all subjects through 48 weeks. No additional treatment disposition data were contained in the 48 week CSR as all subjects had already completed the treatment period at the

time of the original database lock. Additional study disposition data regarding the 64 subjects that were still in follow-up at the time of the original database lock revealed that 2 additional letermovir subjects and 1 additional placebo subject discontinued the study prior to Week 48. All three of these additional early study discontinuations were due to death.

Protocol Violations/Deviations

At the time of database lock, 175/376 (46.5%) subjects randomized to the letermovir arm and 103/194 (53.1%) subjects randomized to the placebo arm had one or more protocol deviations. The most common protocol deviation categories were efficacy assessments (115/570, 20.2%), safety assessments (95/570, 16.7%), and visits performed outside of the protocol-specified visit window (54/570, 9.5%). The rate of protocol deviations was balanced between the arms overall.

The Applicant pre-specified the following deviations as those that had the potential to impact the efficacy analyses: 1) <75% compliant with study therapy; 2) >7 consecutive days of study drug interruption; 3) wrong treatment administered; 4) did not have documented seropositivity for CMV; 5) had a history of CMV end-organ disease within 6 months prior to randomization; 6) was CMV viremic before randomization; 7) prohibited medication; 8) had previously participated in this study or any other study involving letermovir; and 9) had previously participated or was concurrently participating in any study involving administration of a CMV vaccine or another CMV investigational agent during the course of this study. Among the 565 randomized and treated subjects, 30 (8.0%) subjects in the letermovir arm and 14 (7.3%) subjects in the placebo arm met one or more of these criteria. These 44 subjects, along with the subjects with CMV viremia on Day 1, were excluded to create the Per Protocol (PP) population. Analyses of the PP population suggest that the primary and secondary efficacy endpoints were not impacted by these protocol deviations. The primary endpoint was met by the PP population with a p-value of <0.0001.

Reviewer comment: The proportion of subjects with one or more protocol deviations was high for this trial (46.5% and 53.1% in the letermovir and placebo arms, respectively). However, most of these deviations were minor. The proportion of subjects experiencing deviations that were considered significant was much lower (8.0% and 7.3% in the letermovir and placebo arms, respectively). This reviewer agrees with the Applicant's conservative criteria for the generation of the PP population. The even distribution of deviations across both arms and the similar efficacy results in the PP and the FAS populations are reassuring and suggest that the deviations were unlikely to have impacted the trial results.

Demographic Characteristics

The following tables describe the baseline demographic characteristics for subjects in the ASaT population.

Table 5. P001: Demographics of the ASaT Population

	Letermovir N = 373 n (%)	Placebo N = 192 n (%)	Total N = 565 n (%)
SEX			
Male	211 (56.6)	116 (60.4)	327 (57.9)
Female	162 (43.4)	76 (39.6)	238 (42.1)
AGE (YEARS)			
Mean (SD)	50.8 (13.4)	50.8 (14.8)	50.8 (13.9)
Median	53	54	54
Min, Max	18, 75	19, 78	18, 78
AGE GROUP			
>= 18 <= 35	60 (16.1)	33 (17.2)	93 (16.5)
>= 36 <= 50	103 (27.6)	49 (25.5)	152 (26.9)
>= 51 <= 64	154 (41.3)	78 (40.6)	232 (41.1)
>= 65 <= 74	55 (14.7)	30 (15.6)	85 (15.0)
>= 75	1 (0.3)	2 (1.0)	3 (0.5)
RACE			
White	301 (80.7)	161 (83.9)	462 (81.8)
Black	8 (2.1)	4 (2.1)	12 (2.1)
Asian	40 (10.7)	18 (9.4)	58 (10.3)
American Indian	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian	1 (0.3)	0 (0.0)	1 (0.2)
Other	22 (5.9)	9 (4.7)	31 (5.5)
Missing Race	1 (0.3)	0 (0.0)	1 (0.2)
ETHNICITY			
Hispanic	30 (8.0)	10 (5.2)	40 (7.1)
Non-Hispanic	337 (90.3)	177 (92.2)	514 (91.0)
Missing Ethnicity	6 (1.6)	5 (2.6)	11 (1.9)
REGION			
Asia-Pacific	37 (9.9)	16 (8.3)	53 (9.4)
Europe	185 (49.6)	97 (50.5)	282 (49.9)
Latin America	7 (1.9)	2 (1.0)	9 (1.6)
North America	144 (38.6)	77 (40.1)	221 (39.1)

Source: ADSL dataset

As shown in the table, the trial was generally representative of the HSCT population with equal enrollment of both sexes and participation by subjects from a range of age groups, races/ethnicities, and regions. One notable exception is the very limited number of black subjects (12 subjects overall).

Reviewer comment: A PMR may be indicated to better evaluate the safety and efficacy of letermovir in black transplant recipients. It would likely be feasible to enroll a higher proportion of black subjects in the anticipated trial in renal transplant recipients, given that some of the most common causes of end-stage renal disease (e.g., diabetes and hypertension) are prevalent in the African American population.

Table 6. P001: Baseline Disease Characteristics of the ASaT Population

	Letermovir N = 373 n (%)	Placebo N = 192 n (%)	Total N = 565 n (%)
CMV RISK STRATA			
High risk	121 (32.4)	54 (28.1)	175 (31.0)
Low risk	252 (67.6)	138 (71.9)	390 (69.0)
DONOR CMV SEROSTATUS			
Negative	139 (37.3)	78 (40.6)	217 (38.4)
Positive	229 (61.4)	114 (59.4)	343 (60.7)
Unknown	5 (1.3)	0 (0.0)	5 (0.9)
REASON FOR TRANSPLANT			
Acute lymphocytic leukemia	35 (9.4%)	17 (8.9%)	52 (9.2)
Acute myeloid leukemia	142 (38.1%)	72 (37.5%)	214 (37.9)
Aplastic anemia	9 (2.4%)	11 (5.7%)	20 (3.5)
Chronic lymphocytic leukemia	10 (2.7%)	4 (2.1%)	14 (2.5)
Chronic myeloid leukemia	17 (4.6%)	6 (3.1%)	23 (4.1)
Lymphoma	47 (12.6%)	28 14.6%)	75 (13.3)
Myelodysplastic syndrome	63 (16.9%)	22 (11.5%)	85 (15.0)
Myelofibrosis	9 (2.4%)	6 (3.1%)	15 (2.7)
Plasma cell myeloma	14 (3.8%)	10 (5.2%)	24 (4.2)
Other	27 (7.2%)	16 (8.3%)	43 (7.6)
DONOR TYPE			
Matched related	127 (34.0)	64 (33.3)	191 (33.8)
Matched unrelated	138 (37.0)	80 (41.7)	218 (38.6)
Mismatched related	57 (15.3)	22 (11.5)	79 (14.0)
Mismatched unrelated	51 (13.7)	26 (13.5)	77 (13.6)
STEM CELL SOURCE			
Bone marrow	82 (22.0)	47 (24.5)	129 (22.8)
Cord blood	12 (3.2)	11 (5.7)	23 (4.1)
Peripheral blood	279 (74.8)	134 (69.8)	413 (73.1)
ENGRAFTED AT BASELINE			
Yes	132 (35.4)	75 (39.1)	207 (36.6)
No	237 (63.5)	115 (59.9)	352 (62.3)

NA*	4 (1.1)	2 (1.0)	6 (1.1)
CONDITIONING REGIMEN			
Myeloablative	186 (49.9)	97 (50.5)	283 (50.0)
Non-myeloablative	95 (25.5)	41 (21.4)	136 (24.1)
Reduced intensity	92 (24.7)	54 (28.1)	146 (25.8)
ALEMTUZAMAB USE			
Yes	12 (3.2)	11 (5.7)	23 (4.1)
No	361 (96.8)	181 (94.3)	542 (95.9)
ANTITHYMOGLOBULIN USE			
Yes	138 (37.0)	58 (30.2)	196 (34.7)
No	235 (63.0)	134 (69.8)	369 (65.3)

Source: ADSL dataset
*NA = not applicable. Subject's absolute neutrophil count did not go below 500/mm^3 at any point after transplantation due to the conditioning regimen received.

Overall, the two arms were well-matched with regards to baseline disease characteristics. There were more letermovir subjects in the high risk strata and more letermovir subjects received antithymoglobulin. Conversely, more placebo subjects received cord blood transplants. Subjects in the placebo arm were also more likely to be engrafted at baseline.

Reviewer comment: The imbalances described above were relatively small in magnitude. Some of the imbalances may have led to an increase in CMV risk in the letermovir arm (e.g. larger proportion of high risk subjects) and others were more likely to be associated with increased CMV risk in the placebo arm (e.g. larger proportion of subjects receiving a cord blood transplant). This reviewer believes that the small imbalances likely cancelled each other out and were unlikely to have impacted the results of this study.

Treatment Compliance and Concomitant Medications

Letermovir treatment adherence was reported by the Applicant as the percent compliance (number of days on therapy/number of days should be on therapy x 100). The percent compliance was based on subjects' own report of doses taken which they recorded in an electronic diary. Treatment adherence was high in both arms with a mean percent compliance of 98.2% and 98.3% in the letermovir and placebo arms, respectively. Percent compliance < 75% was uncommon in both arms (2.4% and 2.1% of the letermovir and placebo arms, respectively).

The applicant's analysis of concomitant medications was reviewed. The proportion of subjects in each arm who received specific immunosuppressive drugs during the treatment phase is shown in the table below. No notable differences between arms were detected. Of particular interest, 43 (11.5%) of letermovir subjects and 30 (15.6%) of placebo subjects used an mTOR inhibitor (sirolimus or everolimus) at some point during the treatment phase of the study.

Notably, this class of immunosuppressants has been associated with reduced rates of CMV infection [7].

Table 7. P001: Concomitant Immunosuppressive Drug Use (Treatment Phase Only)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		192		565	
Calcineurin Inhibitors	**353**	**(94.6)**	**179**	**(93.2)**	**532**	**(94.2)**
Cyclosporin A	193	(51.7)	100	(52.1)	293	(51.9)
Tacrolimus	174	(46.6)	86	(44.8)	260	(46.0)
Selected Immunosuppressants	**161**	**(43.2)**	**81**	**(42.2)**	**242**	**(42.8)**
Everolimus	7	(1.9)	3	(1.6)	10	(1.8)
Leflunomide	1	(0.3)	0	(0.0)	1	(0.2)
Mycophenolate[†]	139	(37.3)	67	(34.9)	206	(36.5)
Sirolimus	36	(9.7)	27	(14.1)	63	(11.2)
Systemic Corticosteroid	**246**	**(66.0)**	**122**	**(63.5)**	**368**	**(65.1)**

[†] Mycophenolate includes mycophenolate mofetil, mycophenolate mofetil HCl, mycophenolate sodium, and mycophenolic acid.
Every subject is counted a single time for each applicable specific Concomitant immunosuppressant medication. A subject with multiple Concomitant immunosuppressant medication within a medication category is counted a single time for that category.
An immunosuppressant medication class or specific immunosuppressant medication appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with cyclosporin A.
n (%) = Number (percent) of subjects in each sub-category.

Source: Applicant P001V01 CSR

Reviewer Comment: That mTOR inhibitor use was higher in the placebo arm compared to the letermovir arm is reassuring. Had there been more mTOR inhibitor use in the letermovir arm than in the placebo arm, this could have been viewed as potentially contributing to the lower rate of CMV infection observed in the letermovir arm.

Additionally, the proportions of subjects who received antithymoglobulin and alemtuzamab either prior to study drug or concomitantly with study drug were similar, with a slightly higher proportion of letermovir subjects receiving each of these agents compared to placebo subjects (see **Table 6** above).

Reviewer Comment: The above immunosuppression data do not provide the complete picture regarding immunosuppression dosing, immunosuppression changes in response to infection and GVHD, or the overall net degree of immunosuppression in subjects. However, these data suggest that in general, immunosuppression prescribing practices were similar across arms.

Efficacy Results – Primary Endpoint

For Trial P001, the primary efficacy endpoint was the proportion of subjects with clinically

significant CMV infection through Week 24 post-transplant. This was a composite endpoint and could be met by the occurrence of either one of the following:

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

The primary efficacy results are displayed in the table below.

Table 8. P001 Primary Efficacy Analysis: Clinically Significant CMV Infection Through Week 24

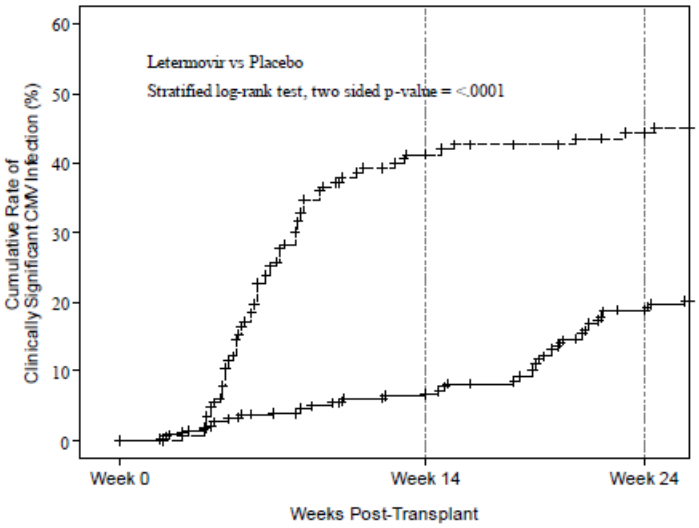
Efficacy Parameter	Letermovir N = 325	Placebo N = 170	Difference (95% CI), p-value
Overall Failures[+]	122 (37.5%)	103 (60.6%)	-23.5 (-32.5, -14.6), <0.001
Clinically Significant CMV Infection	57 (17.5%)	71 (41.8%)	-
Initiation of PET*	52 (16.0%)	68 (40.0%)	-
CMV End-Organ Disease	5 (1.5%)	3 (1.8%)	-
Discontinued from Study	56 (17.2%)	27 (15.9%)	-
Missing Outcome	9 (2.8%)	5 (2.9%)	-

Source: ADEFF, with statistical analysis by Dr. Fraser Smith
[+]Missing data handled using a non-complete = Failure (NC = F) approach
*Regardless of viral load

Reviewer Comment: In the course of the review, two subjects who appeared to have met the criteria for clinically significant CMV infection by Week 24, but for an unclear reason were not reported as having had clinically significant CMV infection, were identified. Subject 0165-102092 initiated PET for CMV viremia on Day 163. The subject's maximum viral load as measured by the central laboratory was 213 copies/mL and therefore did not surpass the predefined threshold for this low risk subject. However, the Applicant's primary approach to assessing the primary endpoint was to include all subjects who started PET, regardless of the CMV viral load, as failures. Subject 0110-100231 had a CMV viral load of 532 copies/mL on Day 125 and was started on PET on Day 132. However, this subject was also considered a success. Both of these subjects were in the letermovir arm. However, given the highly significant p-value, adding two additional failures to the letermovir arm does not impact the interpretation of the primary efficacy endpoint (p-value remains <0.0001).

The Applicant also conducted a time to onset of clinically significant CMV infection through Week 24 analysis which is displayed in the figure below.

Figure 1. P001: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 (FAS population)



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)

Source: Applicant's P001 CSR

Reviewer Comment: This figure demonstrates the robust efficacy of letermovir through Week 24 post-transplantation. However, it should be noted that between Week 14 (when study drug was discontinued) and Week 24, the difference in efficacy decreases in magnitude. The occurrence of late CMV-infection following letermovir discontinuation suggests that some subjects may have benefited from a longer period of prophylaxis. These subjects may be subjects being treated for GVHD and subjects with delayed restoration of CMV-specific immunity. Future studies to define a potential subset of subjects who may benefit from a longer period of prophylaxis would be of interest.

The majority of subjects who experienced clinically significant CMV infection had viremia resulting in the initiation of PET, not CMV end-organ disease. CMV end-organ disease was rare and occurred in a similar proportion of subjects in each arm. The definitive diagnosis of CMV disease requires both clinical signs/symptoms and detection of CMV in tissue (except in the case of CMV retinitis where clinical signs and symptoms are sufficient). All reported cases of CMV end-organ disease were evaluated by a blinded, independent Clinical Adjudication Committee (CAC). In cases where there was disagreement between the CAC and the investigator, the CAC's decision took precedence. The CAC used pre-specified definitions of end-organ disease, based on the definitions published by Ljungman, et al in 2002, to determine if a case was or was not consistent with CMV end-organ disease [6]. In 2017, the definitions for CMV disease were updated by The CMV Drug Development Forum, with input from DAVP [8].

Although the Trial P001 protocol was developed prior to the publication of these revised definitions, the definitions used by the CAC are similar to those recently published. One notable difference is that the criteria used by the CAC do not incorporate the categorization of cases as proven, probable, or possible as the more recent definitions do. As the criteria used by the CAC required that subjects have both appropriate symptoms and detectable CMV in relevant tissue samples, the cases of adjudicated CMV infection included in the discussion and table below are consistent with the proven category of CMV disease in the new definitions.

Through Week 24, there were 10 subjects identified with potential CMV end-organ disease. Of these, 8 were confirmed to have end-organ disease by the CAC. Five cases were in the letermovir arm and 3 cases were in the placebo arm. Onset of confirmed CMV end-organ disease occurred from Study Day 17 to 159 (mean time to onset = 101 ± 55 days). Four of the 5 cases of CMV end organ disease in the letermovir arm occurred after completion of letermovir prophylaxis. The two cases that were determined by the CAC to not be representative of CMV end-organ disease were a case of possible CMV pneumonia in the letermovir arm and a case of CMV hepatitis in the placebo arm. The 8 confirmed cases are summarized in the table below.

Table 9. P001: Subjects with CAC Confirmed CMV End-Organ Disease through Week 24

Subject	Risk Strata	Day of CMV Onset[+]	CMV Disease	Peak Plasma CMV DNA (copies/mL)*	On-Study GVHD	End of Study Status
Letermovir						
0033-100165	High	144	GI	1293	No	Subject completed study. Initial CMV AE resolved by Day 166. However, subject had recurrent viremia on Day 281.
0071-100364	High	133	GI	DNQ	Yes	Subject withdrew from study on Day 143. CMV infection was resolving at that time.
0110-101851	Low	119	GI	41084	Yes	Unclear when CMV resolved as not reported as an AE. Subject completed study on Day 322.
0140-102024	Low	32	GI	DNQ	Yes	**Died** on Day 129 due to *P. aeruginosa* pneumonia.
0091-102193	Low	135	GI	21190	Yes	Study completed on Day 183. At that time, CMV

						infection was resolved.
Placebo						
0020-101645	Low	159	GI	1865	No	Unclear when CMV resolved as not reported as an AE. Study completed on Day 324.
0140-101805	Low	65	GI	235	Yes	CMV infection resolved on Day 162. Study participation was completed on Day 334.
0041-101820	Low	17	GI	7660	Yes	**Died** on Day 18 from *Enterobacter cloacae* septic shock.

Source: ADSL dataset and narratives.
[+]CMV dates based on reported AE dates (in cases where CMV infection not reported as an AE, viral load data and medication records were used to determine timing of infection).
*Central lab results.
DNQ, detected, not quantifiable; GI, gastrointestinal

All confirmed cases of end-organ disease through Week 24 involved the gastrointestinal tract. No CMV disease involving other organs was confirmed by the CAC. Surprisingly, only two of the subjects who experienced end-organ disease were categorized as high-risk at enrollment, though both of these subjects were in the letermovir arm. The two high risk subjects were classified as high risk based on HLA mismatch (one related, one unrelated). Only one subject (0041-101820) had baseline GVHD (< Grade 2) at enrollment; however, 6/8 (75%) subjects with end-organ disease also experienced GVHD AEs while on study. All 6 of these subjects were treated for GVHD with various combinations of corticosteroids and immunosuppressive agents prior to the diagnosis of CMV infection. Of unclear significance, all cases of CMV end-organ disease occurred in men.

Reviewer comment: The occurrence of only gastrointestinal CMV disease may be attributable to the fact that gastrointestinal disease is one of the most common manifestations of CMV end-organ disease among transplant recipients.

Additional details regarding each of the cases of confirmed CMV disease are provided in the following brief narratives.

- 0020-101645 (placebo): This is a 54 year-old man with a history of CML. On study Day 157, he developed diarrhea and abdominal pain. Endoscopy was performed and immunohistochemical staining of the terminal ileum and colon was positive for CMV. On the same day his plasma CMV DNA level was 1865 copies/mL. Study medication had already been discontinued on Day 101. He received IV ganciclovir from Day 172 to Day

220 and was then switched to valganciclovir. He remained on valganciclovir through the end of the study (Day 324). After the initial viral load of 1865 copies/mL, his viral load fluctuated between undetectable and detectable but not quantifiable for the remainder of the study. The CAC confirmed that this case was representative of gastrointestinal CMV end-organ disease. This subject was not reported to have had GVHD.

- 0033-100165 (letermovir): This is a 62 year-old man who underwent HSCT for a plasma cell myeloma. He had an uneventful early post-transplant course, completing the planned letermovir course on Day 84. Then on Day 127 he was found to have a CMV DNA level of 328 copies/mL. By Day 135 the CMV viral load had increased to 1293 copies/mL and he was started on foscarnet. He subsequently developed diarrhea and underwent endoscopy. Immunohistochemical staining of a rectal biopsy was positive for CMV. The CAC confirmed the diagnosis of gastrointestinal CMV. The initial event of CMV infection was considered resolved on Day 166. However, subject did experience additional episodes of CMV viremia for which he was treated with valganciclovir. These episodes were not discussed in the narrative provided by the Applicant.
- 0071-100364 (letermovir): This is a 38 year-old man with a history of myelodysplastic syndrome. He experienced moderate GVHD from Day 49 to 77. He completed his planned letermovir course on Day 83. Then on Day 140 he presented with abdominal pain and diarrhea. Plasma CMV DNA level at that time was detected but not quantifiable. However, biopsy specimens from a sigmoidoscopy showed active colitis with immunohistochemical confirmation of CMV infection. On Day 143 he was started on ganciclovir. On that same day, the subject withdrew his consent to participate in the study. No additional information regarding CMV PCR results or clinical outcome is available. The CAC confirmed that this subject had gastrointestinal CMV disease.
- 0091-102193 (letermovir): This is a 61 year-old man with a history of AML who experienced a mild episode of GVHD from Days 46 to 75. His letermovir treatment was completed on Day 94. He was then hospitalized for an SAE of CMV infection starting on Day 135. Upon hospitalization, he noted 1 week of diarrhea and abdominal pain. He had had low level CMV viremia (472 copies/mL) on Day 123. The viral load then jumped to 54,654 copies/mL (peak) on Day 138. Biopsy specimens obtained via flexible sigmoidoscopy on Day 140 were positive for CMV on histopathologic analysis. He was started on foscarnet initially on Day 135 and then switched back and forth between foscarnet and ganciclovir several times until Day 183 when the CMV event was considered resolved. The CAC agreed with the designation of gastrointestinal CMV disease.
- 0110-101851 (letermovir): This is a 53 year old man with plasma cell myeloma. He had a GVHD SAE from Day 38-62. He completed letermovir therapy on Day 97. Then on Day 119 he was hospitalized with CMV viremia, fever, abdominal pain, and mucous in the stools. Colonoscopy was performed on Day 125 and immunohistochemical staining of biopsy specimens showed active CMV colitis. His CMV viral load peaked at 41,084 copies/mL on Day 139. He was first treated with ganciclovir (Day 128-139), then

foscarnet (Day 139-149), and then valganciclovir (Day 149-175). The CAC agreed that the subject had gastrointestinal CMV disease.

- 0140-101805 (placebo): This is a 58 year-old man with a history of myelodysplastic syndrome. He experienced a moderate AE of GVHD starting on Day 37. He then developed nausea and abdominal pain on Day 43, for which he underwent endoscopy on Day 65. Immunohistochemical staining of samples from the gastric antrum were positive for CMV. His peak plasma viral load was 235 copies/mL on Day 87. Letermovir wasn't discontinued until Day 93. He then received ganciclovir from Day 94 to Day 108, followed by valganciclovir through Day 162, at which time the CMV event was considered resolved. Of note, he experienced a second episode of GVHD starting on Day 113, which was unresolved at the end of the study. The CAC confirmed this as a case of gastrointestinal CMV disease.
- 0041-101820 (placebo): A 63 year-old man underwent HSCT for AML. He was hospitalized on Day 11 with nausea, vomiting, and liver and kidney dysfunction. He was reported as experiencing an SAE of GVHD on the day of hospitalization. Subsequently, study drug was discontinued on Day 12. On Day 15 he was found to have a CMV DNA level of 7,660 copies/mL. On Day 17 he underwent colonoscopy and both immunohistochemical and molecular testing of colon and rectal tissue specimens were positive for CMV. Later, on Day 17, he developed *Enterobacter cloacae* bacteremia and septic shock, which was ultimately fatal on Day 18. The subject had had additional bacterial species isolated from unspecified sources. The CAC confirmed the diagnosis of gastrointestinal CMV disease.

  Reviewer comment: The presence of gram negative (potentially polymicrobial) bacteremia suggests that gut translocation was the source of the fatal septic event. This translocation was likely due to colonic inflammation from CMV colitis. Therefore CMV infection may have been indirectly responsible for this death.

- 0140-102024 (letermovir): This was a 38 year old man with a history of non-Hodgkin's lymphoma. He developed GVHD on Day 21, for which he was hospitalized on Day 28. While being treated for GVHD, he developed CMV viremia (local lab: 400 copies/mL). On Day 37 he underwent colonoscopy and was found to have both CMV and GVHD. Study medication was discontinued on Day 35 and he started foscarnet on Day 36. He remained on foscarnet nearly continuously, until Day 92 when he was switched to cidofovir. He never had quantifiable CMV viremia as measured by the central lab. On Day 84 he was diagnosed with pneumonia, ultimately determined to be due to *Pseudomonas*. He died on Day 129 and pneumonia was considered to be the cause of death. Both the CMV disease and GVHD were considered ongoing at the last study contact. The CAC agreed that this case represented gastrointestinal CMV disease.

There were 3 additional subjects (0126-101773 (letermovir), 0147-100022 (letermovir), and

0059-102018 (placebo)) with investigator-reported end-organ disease through Week 24. All three of these subjects had CMV detected on Day 1 and therefore were not included in the FAS population. These cases were not evaluated by the CAC. There is insufficient information provided regarding these cases for this reviewer to make any further assessments.

Efficacy Results – Secondary and other relevant endpoints

The results of the key secondary endpoint analyses for Trial P001 are presented in the Table below.

Table 10. P001: Key Secondary Efficacy Endpoints

Efficacy Parameter	Letermovir N = 325	Placebo N = 170	Difference (95% CI)	p-value
Clinically Significant CMV Infection Through Week 14*	62 (19%)	85 (50%)	-31% (-40, -23)	<0.0001
CMV End-Organ Disease Through Week 14[+]	1 (<1%)	2 (1%)	-1% (-4, 2)	0.2258
CMV End-Organ Disease Through Week 24[+]	5 (2%)	3 (2%)	-0.4% (-4, 3)	0.4056
Initiation of PET for CMV Viremia Through Week 14*	61 (19%)	84 (49%)	-23% (-32, -14)	<0.0001
Initiation of PET for CMV Viremia Through Week 24*	119 (37%)	101 (59%)	-31% (-40, -22)	<0.0001

Source: ADEFF (confidence intervals and p-values from statistical review and Applicant's CSR)
*Missing data handled using NC = F approach
[+] Missing data handled using data as observed (DAO) approach

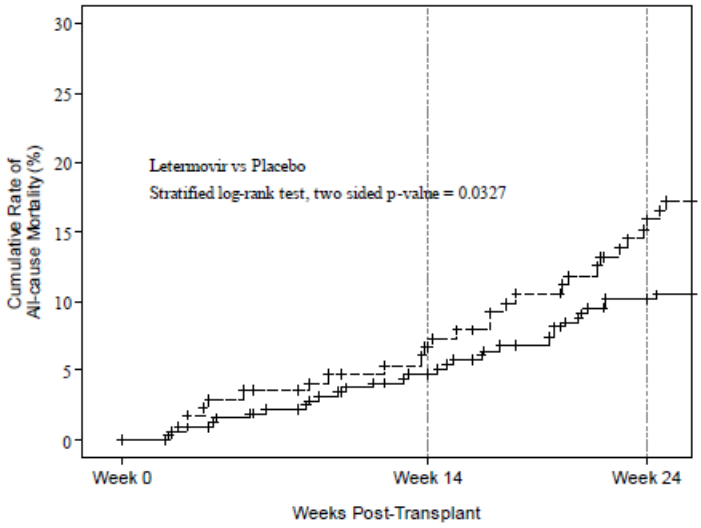
As shown in the table above, the rate of CMV end-organ disease was similarly low in both arms. This is likely due to early initiation of PET following detection of CMV viremia, thus preventing the development of CMV end-organ disease in both arms. All other secondary endpoints were robustly met by letermovir. Of note, though the rate of clinically significant CMV infection through Week 14 was significantly lower in the letermovir arm than the placebo arm, breakthrough infections did occur in letermovir subjects. The majority of letermovir subjects classified as having clinically significant CMV infection through Week 14 had missing data (a NC = failure approach was used for missing data). However, there were 24 (7.4%) letermovir subjects who developed CMV infection while on-treatment.

Mortality

Mortality at 14, 24, and 48 weeks post-transplant was a pre-specified exploratory endpoint. The Applicant's Kaplan-Maier plot for all-cause mortality is presented below. As shown, the

cumulative rate of all-cause mortality at Week 24 was 10.2% in the letermovir arm compared to 15.9% in the placebo arm (two-sided p-value = 0.0327).

Figure 2. P001: Kaplan-Meier Plot of Time to All-cause Mortality



No. at risk: KM estimates % (95% CI)			
Letermovir	325	290: 4.8 (2.4, 7.2)	262: 10.2 (6.8, 13.6)
Placebo	170	147: 6.7 (2.9, 10.5)	125: 15.9 (10.2, 21.6)

Source: Applicant's P001 CSR

When time to all-cause mortality was assessed at Week 48, the event rate was still lower in the letermovir arm (20.9%) compared to the placebo arm (25.5%), but the difference was no longer statistically significant (two sided p-value = 0.1224). Please see the Section on Data Quality and Integrity below for a revised all-cause mortality analysis based on additional data received late in the NDA review cycle. These additional data change the p-values slightly but do not change the overall interpretation of the study.

Reviewer Comment: This reviewer does not find the loss of statistical significance of the mortality benefit at Week 48 to be worrisome. It is anticipated that this far out from transplantation, subjects will be at risk of death from a variety of causes, namely relapsed malignancy, infection, and GVHD. Preventing CMV infection may indirectly reduce the risk of infection and GVHD, but not malignancy. Further, the direct and indirect benefits of preventing CMV infection are likely dampened by Week 48, as by this time point subjects will have been off study drug for 34 weeks.

In addition to looking at all-cause mortality, the Applicant assessed CMV-related mortality and non-relapse mortality as exploratory endpoints. CMV-related mortality was defined as death in any subject who met the primary endpoint (clinically significant CMV infection by Week 24). In time to event analyses of the FAS population, the event rate for CMV-related mortality was significantly lower in the letermovir arm compared to the placebo arm at both 24 weeks (0.7 % vs 9.1%, two-sided p-value < 0.0001) and 48 weeks (3.6% vs. 16.0%, two-sided p-value < 0.0001). Non-relapse mortality was defined as death due to any reason other than the primary condition for which the transplant was performed. Using a time to event analysis at both Week 24 and 48, the rate of non-relapse mortality was numerically, but not statistically lower in the letermovir arm (6.9% vs 11.7% at Week 24 in the letermovir and placebo arms, respectively; and 13.7% vs 17.8% at Week 48 in the letermovir and placebo arms, respectively).

Reviewer Comment: This reviewer finds the presentation of the data regarding CMV-related mortality to be misleading. Using the Applicant's definition of CMV-related mortality, cases of CMV-related death frequently demonstrated no apparent association between CMV and death. While the detrimental indirect effects of CMV infection and the toxicity of anti-CMV therapies may be at play in some of these cases, in many instances death was far removed from CMV infection temporally and often the cause of death was relapse of the underlying disease which is unlikely to have been impacted by CMV infection.

Additional Key Exploratory Endpoints

- Proportion of subjects with CMV disease through week 48:

  There were an additional 6 cases (3 in the letermovir arm and 3 in the placebo arm) of investigator-reported CMV end-organ disease occurring between Week 24 and Week 48. These cases were evaluated by the CAC and all 6 subjects were confirmed to have end-organ disease. Therefore, in total, there were 8/325 (2.5%) letermovir subjects and 6/170 (3.5%) placebo subjects in the FAS population with confirmed CMV end-organ disease through Week 48. The additional 6 cases occurring between Week 24 and Week 48 are summarized in the table below.

Table 11. P001: P001: Subjects with CAC Confirmed CMV End-Organ Disease from Week 24 to Week 48

Subject	Risk Strata	Day of CMV Disease Diagnosis	CMV Disease	Prior CMV Infection (Days)[+]	On-Study GVHD	End of Study Status
Letermovir						

0110-100231	High	259	GI	125 - ongoing	Yes	Subject completed the study on Day 343, at which time CMV PCR was DNQ.
0161-100347	High	261	Retinitis	1* - ongoing	Yes	Subject completed the study on Day 317, at which time CMV PCR was DNQ.
0041-101824	Low	201	GI	122 - 243	Yes	CMV disease resolved on Day 243. Subject completed study on Day 317.
Placebo						
0012-100135	High	284	Retinitis	40 – 96 166 - ongoing	Yes	Subject had ganciclovir-resistant CMV infection, potentially involving the lungs and colon in addition to the eyes (not confirmed). Disease was ongoing at last report on Day 323.
0064-102005	Low	310	Pneumonia	16 - ongoing	No	Bronchoalveolar lavage fluid positive for *Aspergillus* and *E. coli* in addition to CMV. Subject **died** of pneumonia on Day 316.
0018-102074	Low	204	GI	N/A	No	Subject **died** on Day 222 from an intracranial hemorrhage. By the time of death, GI symptoms were under control (plasma PCR never quantifiable).

Source: p001v02 ADSL dataset and narratives.
[+]CMV dates based on reported AE dates (when CMV infection not reported as an AE, viral load data and medication records were used to determine timing of infection).
*Subject had a CMV AE starting on Day 1, but central laboratory CMV PCR was negative on Day 1, therefore subject was included in FAS population.

Abbreviations: DNQ, detected not quantifiable; GI, gastrointestinal; GVHD, graft versus host disease.

As seen in cases of CMV end-organ disease occurring in the first 24 weeks, gastrointestinal disease remained the most common manifestation through Week 48. Additionally, 4 of 6 subjects experiencing CMV end-organ disease also had GVHD. While none of the CMV end-organ disease cases appeared to be directly fatal in the first 24 weeks, subject 0064-102005 (placebo) died of pneumonia at Day 316 (Week 45), shortly after being diagnosed with CMV pneumonia (though there were other pathogens detected).

Notably, all but one of the subjects in the table above had experienced earlier episodes of CMV infection (without documented end-organ disease). All of these earlier episodes occurred prior to the assessment of the primary endpoint. Therefore, all of these subjects should have been considered to have met the primary endpoint, but on the basis of the initiation of PET, not on the basis of end-organ disease. As previously mentioned, it appears that letermovir subject 0110-100231 was not counted as having met the primary endpoint, despite the narrative clearly describing the initiation of PET prior to Week 24. Although most subjects with prior episodes of CMV viremia went on to have periods without CMV viremia and without need for anti-CMV therapy between the initial diagnosis of CMV infection and the diagnosis of CMV end-organ disease, the pathology that led to the development of CMV end-organ disease was already in play at the time of the primary end-point assessment.

Reviewer Comment: Whether these subjects were considered to have met the primary endpoint based on CMV viremia or CMV end-organ disease does not impact the primary endpoint results. Nor does it significantly impact the results of the secondary efficacy endpoint 'Proportion of subjects with CMV end-organ disease at Week 24.' If all of the subjects who were viremic prior to Week 24 and developed end-organ disease after Week 24 were considered to have had end-organ disease at Week 24, the proportion of subjects meeting this secondary end point would be 8/325 (2.5%) and 5/170 (2.9%) in the letermovir and placebo arms, respectively. The number of subjects experiencing CMV end-organ disease was small and similar between arms, regardless of how these few subjects are categorized.

- Incidence of CMV viremia and PET initiation between Week 24 and Week 48.

  After the primary endpoint was assessed at Week 24, additional cases of CMV viremia with and without PET initiation occurred in both arms. Between Week 24 and Week 48, 52 (16.0%) letermovir subjects and 27 (15.9%) placebo subjects developed CMV viremia (Applicant reports 51 and 26 subjects). The majority of these subjects (38 of the letermovir subjects and 19 of the placebo subjects) had maximum viral loads that were detectable but not quantifiable. Six letermovir subjects and 3 placebo subjects had a maximum CMV viral load ≥ 1,000 copies/mL. The remaining subjects had viral loads > 150 copies/mL and < 1,000

copies/mL. Four letermovir subjects and 0 placebo subjects were reported to have initiated PET during the secondary follow-up period. However, these data appear to have been incompletely captured.

Reviewer Comment: This reviewer does not find the lack of a difference in the rates of CMV viremia between the two arms from Week 24 to Week 48 to be surprising or concerning. It is remarkable that letermovir appeared to be associated with a reduction in the rate of CMV infection and disease that persisted for up to 10 weeks after its discontinuation. It may not be reasonable to expect a drug to exert an effect on CMV infections for > 6 months after discontinuation. In subjects who remain at high risk for CMV infection, longer periods of prophylaxis may be warranted. A study comparing 100 days vs 200 days of letermovir in HSCT recipients (as was performed in renal transplant recipients receiving valganciclovir) may help address this question.

- Antiviral resistance to letermovir in prophylaxis failures.

Analysis of amino acid substitutions occurring in all subjects who had detectable CMV viremia in Trial P001 was attempted. DNA sequence results for UL56 and UL89 were used for the primary genotyping analysis as these are genes encoding subunits of CMV DNA terminase. In the FAS population of Trial P001 there were 24/325 (7.4%) letermovir subjects and 65/170 (38.2%) placebo subjects who experienced on-treatment virologic failure. An additional 28 letermovir subjects and 3 placebo subjects experienced virologic failure following completion of the treatment phase. Unfortunately, the laboratory originally chosen to perform the genotypic analyses had poor assay sensitivity. This was particularly problematic given the low CMV DNA thresholds used for the initiation of anti-CMV preemptive therapy. Therefore, a new lab was chosen after the study was already underway. In some instances, there was insufficient sample remaining to allow for testing at the second laboratory. Ultimately, there were 30/52 letermovir subjects who experienced virologic failure with genotypic data available.

Amongst the letermovir subjects in the FAS population with complete sequencing data available, there were 3/8 (37.5%) subjects and 0/22 (0%) subjects in the on-treatment virologic failure and off-treatment virologic failure groups, respectively, with amino acid substitutions that have previously been associated with letermovir resistance in cell culture (see Section 4.3).

Reviewer Comment: The fact that the identified resistance-associated substitutions all occurred in subjects with on-treatment virologic failure, suggests that failures occurring between week 14 and 24 were likely not attributable to resistance, but perhaps were due to inadequate immune restoration. Therefore, a prolonged period of prophylaxis may be of benefit in some instances. A trial comparing 100 days vs. 200 days of prophylaxis in HSCT recipients would be of interest.

The following are the resistance associated substitutions that the clinical virology reviewers recommend be included in the letermovir label, along with the reason for inclusion:

- E237G, V236M, and C325W - these are known resistance-associated substitutions in cell culture, and substitutions were only detected in letermovir subjects who experienced on-treatment failure.
- 445-447 SNS deletion and E485G – these substitutions occurred at a high frequency (> 70%) in 2 of 8 letermovir subjects experiencing on-treatment virologic failure.

Please see the Clinical Virology Review by Takashi Komatsu, PhD, for additional details.

- Proportion of subjects with acute and/or chronic GVHD after randomization through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant.

  In Trial P001, GVHD was reported as an AE if it occurred during the treatment period (through Week 16) or if it occurred during a follow-up period but was considered to be a drug-related SAE or a fatal SAE. Otherwise, GVHD events were captured through the Health Outcomes Assessment (HOA) performed at select study visits. GVHD was one of the most common AEs, SAEs, and causes of death reported in this study. Rates of these GVHD-related safety events are discussed in detail in Section 8.4. GVHD was also examined as an exploratory efficacy endpoint. The findings of these efficacy analyses are presented in this section. In the table below, the proportion of FAS subjects experiencing their first episode of acute or chronic GVHD through various time points is displayed.

  The Applicant defined acute GVHD as GVHD occurring prior to Day 100 post-transplant and chronic GVHD as GVHD occurring after Day 100 post-transplant. Acute GVHD was graded on a scale of I – IV, using the Glucksberg grading system. No grading was performed for chronic GVHD.

  Reviewer Comment: Recently, there has been a movement away from categorizing GVHD as acute or chronic based purely on the time from transplant. This change has come in response to the realization that chronic GVHD can occur prior to Day 100 and acute GVHD can occur after Day 100. Therefore, classification based on clinical characteristics rather than time from transplant has become standard. However, this change in the definitions of acute and chronic GVHD is unlikely to have a meaningful impact on the interpretation of this study as the rates of GVHD overall are similar between the arms (slightly higher in the placebo arm).

Table 12. P001: The Proportion of Subjects Experiencing GVHD through Weeks 14, 24, and 48 Post-Transplant (FAS population)

GVHD Parameter	Letermovir N=325 N (%)	Placebo N=170 N (%)
Through Week 14		
Acute GVHD	126 (38.8%)	70 (41.2%)
Grade I	57 (17.5%)	29 (17.1%)
Grade II	49 (15.1%)	29 (17.1%)
Grade III	16 (4.9%)	8 (4.7%)
Grade IV	6 (1.8%)	4 (2.4%)
Chronic GVHD	0 (0.0%)	0 (0.0%)
Through Week 24		
Acute GVHD	146 (44.9%)	82 (48.2%)
Grade I	64 (19.7%)	35 (20.6%)
Grade II	57 (17.5%)	30 (17.6%)
Grade III	18 (5.5%)	10 (5.9%)
Grade IV	7 (2.2%)	7 (4.1%)
Chronic GVHD	32 (9.8%)	20 (11.8%)
Through Week 48		
Acute GVHD	158 (48.6%)	85 (50%)
Grade I	73 (22.5%)	37 (21.76)
Grade II	57 (17.5%)	30 (17.7%)
Grade III	20 (6.2%)	10 (5.9%)
Grade IV	8 (2.5%)	8 (4.7%)
Chronic GVHD	71 (21.8%)	40 (23.5%)

Source: P001V02 ADEFF dataset
Some subjects experienced both acute and chronic GVHD and are counted under both categories.

As expected, the proportion of GVHD cases that were chronic increased over the course of the study, though acute GVHD remained more common than chronic GVHD for the duration of the study. At each of the time points above, the proportion of subjects with acute and chronic GVHD was slightly higher in the placebo arm compared to the letermovir arm. Analyzing acute GVHD grades at each time point, it appears that approximately half of the acute GVHD cases were Grade II or greater in each arm. Grade III and IV acute GVHD was uncommon overall. The proportion of subjects with Grade III GVHD was very similar in both arms. However, there was a slightly larger proportion of subjects with Grade IV acute GVHD in the placebo arm. In both the letermovir arm and the placebo arm, the skin was the most common site for acute GVHD, followed by the gastrointestinal tract, then the liver.

Reviewer Comment: Overall, there was a trend towards an increase in frequency and severity of GVHD events in the placebo arm compared to the letermovir arm. The

magnitude of this difference was small and of unclear clinical significance. An association between GVHD and CMV infection among HSCT recipients is well-known, though incompletely understood. It is generally accepted that the treatment of GVHD and perhaps GVHD itself is associated with the development of CMV infection. That the relationship extends the other direction (i.e. that CMV infection can play a role in the development of GVHD) has also been proposed in the literature, but this relationship is less established [9].

- Proportion of subjects with opportunistic infection other than CMV infection through Week 14 post-transplant, Week 24 post-transplant, and Week 48 post-transplant.

  Infection is a major cause of morbidity and mortality in the post-transplant period. During this time, transplant recipients' immune system is markedly suppressed leaving them vulnerable to a host of infections. Infections that are more common in the setting of immunosuppression are referred to as opportunistic infections (OIs). OIs are theorized to be a negative, indirect consequence of CMV infection. Additionally, the use of currently available anti-CMV therapies, namely ganciclovir and valganciclovir, has been associated with neutropenia, which is known to be associated with increased rates of bacterial sepsis and invasive fungal infections [10]. Therefore, the rate of OIs is included as an efficacy endpoint. A broad range of bacterial, viral, fungal, and parasitic infections are encompassed by the term OI. For the purposes of this trial, any infection that would be considered an OI in the HSCT setting was considered to be an OI. However, CMV infection was not reported as an OI, but as an AE. During the treatment period, all OIs were reported as AEs. After Week 16, only OIs that were SAEs were reported as AEs. Any OI occurring after Week 16 that was not required to be reported as an AE was reported separately as an OI.

  The Applicant performed analyses of individual OIs and categories of OIs (i.e. bacterial, fungal, etc.) at 14, 24, and 48 Weeks. See a summary of these findings in the table below.

Table 13. P001: Opportunistic Infections (OIs) through Weeks 14, 24, and 48 Post-Transplant (FAS Population)

Opportunistic Infection Category	Through Week 14		Through Week 24		Through Week 48	
	Letermovir N=325	Placebo N=170	Letermovir N=325	Placebo N=170	Letermovir N=325	Placebo N=170
Any OI	109 (33.5%)	52 (30.6%)	117 (36.0%)	58 (34.1%)	143 (44.0%)	72 (42.4%)
Bacterial OI	67 (20.6%)	34 (20.0%)	72 (22.2%)	38 (22.4%)	97 (29.8%)	45 (26.5%)
Fungal OI	22 (6.8%)	4 (2.4%)	26 (8.0%)	8 (4.7%)	34 (10.5%)	20 (11.8%)
Viral OI	50 (15.4%)	27 (15.9%)	52 (16.0%)	28 (16.5%)	71 (21.8%)	36 (21.2%)
Parasitic OI	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)

Source: Applicant's P001v01 and P001v02 CSRs

While the proportion of subjects experiencing bacterial, parasitic, and viral OIs is similar across arms, the proportion of subjects experiencing fungal OIs is markedly higher in the letermovir arm compared to the placebo arm at both 14 and 24 weeks post-transplant.

Many of the events included in the OI analyses displayed above were not clinically relevant as OIs in the HSCT population (e.g., urinary tract infections, Clostridium difficile diarrhea, etc.). Therefore, the Applicant created a narrower list of OIs of interest (selected OIs). These selected OIs were the focus of this Reviewer's analysis. The proportion of subjects experiencing these selected OIs is presented in the table below.

Table 14. P001: Selected Opportunistic Infections (OIs) through Week 24 (FAS Population)

Selected OI Category and Coded Term	Letermovir N = 324	Placebo N = 170
Any Select OI	67 (20.6%)	40 (23.5%)
Bacterial OI	44 (13.5%)	26 (15.3%)
Bacteremia	32 (9.8%)	19 (11.2%)
Pneumonia	5 (1.5%)	2 (1.2%)
Sepsis	7 (2.2%)	8 (4.7%)
Fungal OI	14 (4.3%)	9 (5.3%)
Aspergillosis	13 (4.0%)	6 (3.5%)
Mucormycosis	0 (0.0%)	1 (0.6%)
PJP pneumonia	1 (0.3%)	2 (1.2%)
Viral OI	17 (5.2%)	11 (6.5%)
Adenovirus disease	1 (0.3%)	0 (0.0%)
BK virus infection	10 (3.1%)	7 (4.1%)
EBV meningoencephalitis	0 (0.0%)	1 (0.6%)
HHV-6 meningoencephalitis	2 (0.6%)	0 (0.0%)
Influenza	1 (0.3%)	0 (0.0%)
Parainfluenza virus infection	3 (0.9%)	0 (0.0%)
RSV infection	1 (0.3%)	3 (1.8%)
Parasitic OI	0 (0.0%)	1 (0.6%)
Cerebral Toxoplasmosis	0 (0.0%)	1 (0.6%)

Source: OIINT2 dataset

Overall, the proportion of subjects experiencing one or more of the selected OIs was higher in the placebo arm. The proportion of subjects experiencing specific OIs or categories of OIs is similar (< 2% difference) between the treatment arms. The most common selected OIs were bacteremia, BK virus infection, aspergillosis, sepsis, and pneumonia.

Reviewer Comment: When looking at only the selected OIs, the potential increase in events in the letermovir arm that was demonstrated in the overall OI analysis is no longer present. However, the designation of "selected OIs" as performed by the Applicant was somewhat arbitrary. Fungal OIs that were included in the overall OI analysis and not included in the

selected OI analysis consisted of oral candidiasis, vulvovaginal candida, and fungal nail infection. From the efficacy perspective, the prevention of CMV infection/disease by letermovir does not appear to be associated with an associated reduction in non-CMV OIs. The potential safety implications of infections in general in the study population are discussed in detail in Section 8.5.4.

Dose/Dose Response

No association between letermovir exposure (AUC and C_{min}) and the probability of clinically significant CMV infection through Week 24 was seen in Trial P001.

Durability of Response and Persistence of Effect

Following HSCT, the early post-transplant period (the first 100 days) is the period of greatest risk for CMV infection/disease. In Trial P001, subjects received study drug though the period of greatest CMV risk (through Week 14, approximately Day 100). However, the primary endpoint was not assessed until Week 24. The results of this study show that letermovir is effective in the prevention of CMV infection through the period of greatest CMV risk. Importantly, the results also suggest that letermovir provides benefit that persists for some period after treatment is discontinued.

Reviewer comment: That the rate of clinically significant CMV infection remained statistically significantly lower in the letermovir arm 10 weeks after the completion of study drug is quite remarkable. Prior to this study, it was not clear that an anti-CMV drug could exert a durable, off-treatment effect on CMV infection in the face of ongoing immunosuppression and absence of CMV-specific immunity restoration in some subjects. However, it should be noted that between Week 14 and 24, the rate of CMV infection was actually higher in the letermovir arm than the placebo arm. Therefore, it was letermovir's profound impact on CMV infection during the first 14 weeks post-transplant that was responsible for the significant reduction in CMV infection through Week 24. A similar increase in the rate of CMV infection has been observed in renal transplant recipients upon completion of 100 days of valganciclovir prophylaxis. In the case of renal transplant subjects, the occurrence of this "late" CMV infection following the completion of prophylaxis can be overcome by extending the prophylaxis duration to 200 days [11]. CMV seropositive HSCT recipients may also benefit from a longer period of prophylaxis to allow for restoration of CMV-specific immunity. Longer prophylaxis may lead to improved off-treatment durability of response.

Additional Analyses Conducted on the Individual Trial

None

Data Quality and Integrity – Reviewers' Assessment

The overall quality of the data was assessed to be adequate. However, the review team did have some concerns regarding how subjects who discontinued from Trial P001 were accounted for. In particular, in some instances, it was known that a subject who discontinued from the trial went on to die. However, as these deaths occurred post-study and post-study outcomes were not consistently available, the Applicant did not include these deaths in their mortality analyses. In total, there were 87 subjects who discontinued the trial for reasons other than death. In the original application, the outcome of only 11 of these subjects was provided.

The Division first raised concerns regarding the missing vital status of discontinued subjects in the 74-Day Filing Letter. In response, the Applicant worked with investigators and were able to determine the vital status of 58 of the remaining 76 subjects who discontinued the study prematurely, resulting in available vital status data for 547/565 (96.8%) of subjects overall. On July 14, 2017 the Applicant submitted a report including a sensitivity analysis of all-cause mortality at Weeks 24 and 48 among the FAS population using the more complete mortality data. In this sensitivity analysis, the Kaplan-Meier event rate for all-cause mortality at 24 weeks remained significantly lower in the letermovir arm (12.1%) compared to the placebo arm (17.2%)(two-sided p-value=0.0401). As observed in the original analysis of mortality at 48 weeks, there was a trend towards a reduction in all-cause mortality in the letermovir arm that did not reach statistical significance (23.8% vs 27.6% in the letermovir and placebo arms, respectively, two-sided p-value=0.2117).

6.2. Trial P020

6.2.1. Study Design

Overview and Objective

P020 was a Phase 2b, randomized, double-blind, placebo-controlled trial evaluating the safety, tolerability, and antiviral activity of 12 weeks of letermovir therapy in CMV seropositive subjects who had undergone HSCT.

Trial Design

This study was conducted at 19 sites in Germany and the USA from March 30, 2010 through October 17, 2011. HSCT recipients were randomized to receive 1 of 3 letermovir oral doses (60 mg daily, 120 mg daily, or 240 mg daily) or placebo in a 3:1 ratio. Subjects were randomized within 40 days of transplantation and study treatment was administered for 84 days (12 weeks).

Study Endpoints

The primary efficacy endpoint for Trial P020 was CMV prophylaxis failure within the 84-day treatment period. CMV prophylaxis failure was defined as systemic detectable CMV replication (two blood samples positive for CMV DNA at a local laboratory and one confirmatory blood sample from the central laboratory) or the development of CMV end-organ disease. No CMV DNA threshold was specified for the initiation of PET. Time to onset of CMV prophylaxis failure was also assessed as a primary efficacy endpoint.

The secondary efficacy endpoints were:

- Incidence and time to onset of HCMV end-organ disease alone within the 84-day treatment period.
- Incidence and time to onset of systemic detectable HCMV replication alone within the 84-day treatment period.
- Incidence and time to onset of discontinuation of trial medication within the 84-day treatment period.

Statistical Analysis Plan

The Full Analysis Set (FAS) population, which consisted of all randomized subjects who received at least one dose of study treatment and had at least 1 CMV DNA evaluation (from local or central laboratory) after randomization, was pre-specified as the primary population for efficacy analyses. Pairwise Fisher's exact tests for each active treatment group vs. placebo were conducted to assess the primary endpoint. The Safety Set (SS) population consisted of all randomized subjects who received at least one dose of study treatment and was used for all safety analyses.

Please see the Biometrics review by Dr. Fraser Smith for additional details regarding the statistical analysis plan.

Protocol Amendments

The original protocol was submitted on November 24, 2009 and was amended once on June 21, 2011. This amendment included minor, insubstantial revisions only.

6.2.2. Study Results

Patient Disposition

One hundred and sixty-six subjects were screened and 133 subjects were randomized into one of the four treatment arms. Two randomized subjects in the letermovir 120 mg/day arm did not receive any study drug (one subject experienced CMV reactivation prior to treatment and one subject's health deteriorated). These subjects were therefore not included in any of the

safety or efficacy analyses, leaving 131 subjects in the Safety Set (SS) and the Full Analysis Set (FAS). Of note, the SS was defined as subjects who received at least one dose of study drug and the FAS was defined as subjects who received one dose of study drug and had at least one CMV evaluation after randomization. However, the SS and the FAS ultimately consisted of the same subjects. Treatment and study dispositions are presented in the table below.

Table 15. P020: Treatment and Study Disposition

	Letermovir 60 mg/day	Letermovir 120 mg/day	Letermovir 240 mg/day	Placebo
Randomized	33	33	34	33
Treated	33	31	34	33
Treatment Disposition				
Completed treatment	17 (51.5%)	21 (67.7%)	24 (70.6%)	12 (36.4%)
Discontinued treatment	16 (48.5%)	10 (32.3%)	10 (29.4%)	21 (63.6%)
PET initiated	7 (21.2%)	6 (19.4%)	2 (5.9%)	13 (39.4%)
Subject non-compliant	4 (12.1%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
Withdrawal by subject	1 (3.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Adverse event	3 (9.1%)	3 (9.7%)	5 (14.7%)	7 (21.2%)
Death	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Other*	1 (3.0%)	1 (3.2%)	1 (2.9%)	0 (0.0%)
Study Disposition				
Completed study	29 (87.9%)	27 (87.1%)	30 (88.2%)	26 (78.8%)
Discontinued study	4 (12.1%)	4 (12.9%)	4 (11.8)	7 (21.2%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Withdrawal by subject	3 (9.1%)	2 (6.5%)	1 (2.9%)	2 (6.1%)
Adverse event	1 (3.0%)	0 (0.0%)	1 (2.9%)	1 (3.0%)
Death	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (3.0%)
Other+	0 (0.0%)	2 (6.5%)	0 (0.0%)	3 (9.1%)

Source: DS dataset.
The denominator used to calculate percentages is the number of treated subjects in that arm
*Other reasons for treatment discontinuation: 1 subject in letermovir 60 mg/day arm was unblinded due to participation in another study, 1 subject in the letermovir 120 mg/day arm was released from BMT unit and was returning home, and 1 subject in the letermovir 240 mg/day arm had medication stopped by family doctor for hypertension which was reported as a baseline condition in the medical history.
+Other reasons for study discontinuation: 1 subject in the letermovir 120 mg/day arm was discontinued due to CMV replication during the trial, 1 subject in the letermovir 120 mg/day arm was released from BMT unit and returned home, and 3 subjects in the placebo arm were discontinued due to a site error.

Protocol Violations/Deviations

The following were considered major protocol violations and resulted in the exclusion of subjects from the Per Protocol Set (PPS): more than 7 days between screening local laboratory CMV sample date and date of randomization, treatment compliance of < 80%, a gap in treatment of 80 hours or more, use of prohibited medication, and graft vs. host disease grade 2 or higher at randomization. Fourteen (10.7%) subjects in the SS had major protocol violations that resulted in their exclusion from the PPS. Five (15.2%) of these subjects were in the placebo arm and 9 (9.2%) of these subjects were in one of the letermovir arms. The most common major protocol violation was gap in treatment of 80 hours or more, which occurred in 5 (5.1%) letermovir subjects and 1 (3.0%) placebo subject.

Demographic Characteristics

The demographic characteristics of the subjects in the safety population for Trial P020 are presented below. Overall, the arms are well matched. Notable exceptions include an increased proportion of female subjects in the letermovir 60 mg arm and an increased proportion of Hispanic subjects in the letermovir 120 mg arm. As with Trial P001, there were very few black subjects enrolled in Trial P020.

Table 16. P020: Subject Demographic Characteristics of the SS Population

Characteristic	Letermovir 60 mg N = 33	Letermovir 120 mg N = 31	Letermovir 240 mg N = 34	Letermovir All N = 98	Placebo N = 33
SEX					
Male	14 (42.4%)	22 (71.0%)	22 (64.7%)	58 (59.2%)	19 (57.6%)
Female	19 (57.6%)	9 (29.0%)	12 (35.3%)	40 (40.8%)	14 (42.4%)
AGE, YEARS					
Mean (SD)	50.5 (13.0)	51.6 (12.8)	50.7 (11.8)	50.9 (12.4)	51.8 (13.4)
Median	55.0	57.0	53.5	54.5	53.0
Min, Max	24, 69	22, 68	25, 67	22, 69	24, 71
RACE					
White	29 (87.9%)	29 (93.5%)	33 (97.1%)	91 (92.9%)	32 (97.0%)
Black	3 (9.1%)	1 (3.2%)	0 (0.0%)	4 (4.1%)	1 (3.0%)
Asian	1 (3.0%)	1 (3.2%)	1 (2.9%)	3 (3.1%)	0 (0.0%)
ETHNICITY					
Hispanic	0 (0.0%)	5 (16.1%)	2 (5.9%)	7 (7.1%)	3 (9.1%)
Non-Hispanic	33 (100.0%)	26 (83.9%)	31 (91.2%)	90 (91.8%)	30 (90.9%)
Missing	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (1.0%)	0 (0.0%)

Source: ADSL dataset

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics of the subjects in the safety population for Trial P020 are presented in the table below.

Table 17. P020: Subject Baseline Disease Characteristics (SS Population)

Characteristic	Letermovir 60 mg N = 33	Letermovir 120 mg N = 31	Letermovir 240 mg N = 34	Letermovir All N = 98	Placebo N = 33
DONOR CMV SEROSTATUS*					
Negative	20 (60.6%)	14 (45.2%)	13 (38.2%)	47 (48.0%)	14 (42.4%)
Positive	13 (39.4%)	17 (54.8%)	21 (61.8%)	51 (52.0%)	19 (57.6%)
REASON FOR TRANSPLANT					
Acute lymphocytic leukemia	2 (6.1%)	6 (19.4%)	3 (8.8%)	11 (11.2%)	2 (6.1%)
Acute myeloid leukemia	14 (42.4%)	11 (35.5%)	13 (38.2%)	38 (38.8%)	11 (33.3%)
Chronic lymphocytic leukemia	1 (3.0%)	1 (3.2%)	1 (2.9%)	3 (3.1%)	3 (9.1%)
Chronic myeloid leukemia	5 (15.2%)	1 (3.2%)	3 (8.8%)	9 (9.2%)	3 (9.1%)
Hodgkin's lymphoma	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (1.0%)	2 (6.1%)
Non-Hodgkin's lymphoma	3 (9.1%)	6 (19.4%)	6 (17.6%)	15 (15.3%)	5 (15.2%)
Multiple myeloma	3 (9.1%)	2 (6.5%)	3 (8.8%)	8 (8.2%)	0 (0.0%)
Myelodysplastic syndrome	3 (9.1%)	4 (12.9%)	3 (8.8%)	10 (10.2%)	5 (15.2%)
Myeloproliferative disorder	2 (6.1%)	0 (0.0%)	1 (2.9%)	3 (3.1%)	2 (6.1%)
DISEASE STATUS AT TRANSPLANT					
Remission	18 (54.5%)	20 (64.5%)	20 (58.8%)	58 (59.2%)	15 (45.5%)
Active disease	15 (45.5%)	11 (35.5%)	14 (41.2%)	40 (40.8%)	18 (54.5%)
TYPE OF TRANSPLANT					
Matched unrelated	18 (54.5%)	13 (41.9%)	17 (50.0%)	48 (49.0%)	11 (33.3%)
Matched related	15 (45.5%)	18 (58.1%)	17 (50.0%)	50 (51.0%)	22 (66.7%)
STEM CELL SOURCE					
Bone marrow	1 (3.0%)	0 (0.0%)	1 (2.9%)	2 (2.0%)	2 (6.1%)
Peripheral blood	32 (97.0%)	31 (100.0%)	33 (97.1%)	96 (98.0%)	31 (93.9%)

Source: ADSL and HBPCT datasets (this analysis was performed in JMP)
*All subjects were CMV seropositive (R+)

Subjects in the letermovir arms were more likely to have received a transplant from a CMV seronegative donor, to be in remission at the time of transplant, and to have received a matched unrelated donor as compared to the placebo arms.

Reviewer Comment: It is not clear if/how all of the identified differences in baseline disease characteristics may have impacted the risk of CMV infection. It could be predicted that subjects receiving an unrelated transplant would require more immunosuppression and therefore would be at increased risk of CMV infection. The effect of donor CMV seropositivity on CMV reactivation in a CMV seropositive recipient is controversial [1]. However, one study suggested

that CMV seropositive HSCT recipients who receive a CMV seropositive graft are at increased risk for CMV infection, though the infection is generally less severe [12].

Efficacy Results - Primary Endpoint

The primary efficacy endpoint for Trial P020 was CMV prophylaxis failure at Day 84, which was defined as the development of systemic CMV replication and/or CMV end-organ disease, or treatment discontinuation for another reason. The results are presented in the table below.

Table 18. P020: Primary Efficacy Analysis: CMV Prophylaxis Failure Through Day 84 (FAS Population)

Efficacy Parameter	Letermovir 60 mg/day N = 33	Letermovir 120 mg/day N = 31	Letermovir 240 mg/day N = 34	Placebo N = 33
Failure	16 (48.5%)	10 (32.3%)	10 (29.4%)	21 (63.6%)
CMV Prophylaxis Failure	7 (21.2%)	6 (19.4%)	2 (5.9%)	12 (36.4%)
Other discontinuations	9 (27.3%)	4 (12.9%)	8 (23.5%)	9* (27.3%)
OR (95% CI) – placebo arm is reference group	0.5 (0.2, 1.6)	0.3 (0.1, 0.9)	0.2 (0.1, 0.7)	-
p-value	0.321	0.014	0.007	-

Source: ADSL dataset (OR (95% CI) and p-values from Applicant's CSR)
* Subject 201008 in the placebo arm was started on PET, but did not meet the protocol definition of CMV prophylaxis failure as CMV replication was never confirmed by the central laboratory. Therefore, this subject is categorized as an 'other discontinuation'.

As shown above, the two higher doses of letermovir were found to be statistically superior to placebo in the prevention of CMV infection. Importantly, all three doses of letermovir were numerically superior to placebo, with the rate of CMV prophylaxis failure decreasing with increasing letermovir doses. Therefore, the results of Trial P002 demonstrate a dose-response and provide supportive evidence of the efficacy of letermovir for the prevention of CMV infection in HSCT recipients. Of note, there were no cases of CMV end-organ disease in Trial P020. All CMV prophylaxis failures were attributable to CMV replication without confirmed organ involvement.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Letermovir successfully prevented CMV infection in CMV seropositive HSCT recipients in both Trial P001 and P020. Further, in Trial P001, numerous sensitivity analyses showed that letermovir was successful in preventing CMV infection in subpopulations including high risk subjects, low risk subjects, subjects who started PET regardless or CMV viral load, and subjects who started PET only if their CMV viral load surpassed the protocol-defined thresholds (please see the biometrics review by Fraser Smith, PhD for additional details regarding these sensitivity analyses). The Applicant also conducted numerous sensitivity analyses for Trial P020 and the robustness of the data was confirmed in this trial as well.

Reviewer Comment: The low p-values associated with the primary endpoint in both Trial P001 and P020 combined with the robustness of the data demonstrated in sensitivity analyses provides this reviewer with confidence that letermovir is highly effective in the prevention of CMV infection.

7.1.2. Secondary and Other Endpoints

Both Trial P001 and P020 met the secondary efficacy endpoint 'time to clinically significant CMV infection/CMV prophylaxis failure.' Neither trial was able to demonstrate a reduction in CMV end-organ disease associated with letermovir use, as the number of subjects experiencing CMV end-organ disease was very small in both arms. Trial P001 unexpectedly showed that letermovir was associated with a reduction in all-cause mortality at Week 24. No mortality analysis was included in Trial P020.

7.1.3. Subpopulations

Determining whether the efficacy of a drug is consistent across all relevant subpopulations is required by 21 CFR 314.50(d)(5)(v). The table below shows the proportion of subjects in various key demographic and disease characteristic subgroups of interest that had clinically significant CMV infection through Week 24. This table only includes data from P001. As noted above, data from P020 and P001 were not pooled due to the different dosing and the different time points used for the assessment of the primary endpoint.

Table 19. P001: Proportion of Subjects with Clinically Significant CMV Infection through Week 24 Post-transplant in Key Subgroups (FAS Population, NC=F)

	Subjects with Clinically Significant CMV Infection		
Characteristic	Letermovir n/N (%)	Placebo n/N (%)	Difference in % (95%CI)*
Gender			
Male	72/176 (40.9%)	58/104 (55.8%)	-15.7 (-27.2, -3.8)
Female	50/149 (33.6%)	45/66 (68.2%)	-34.8 (-48.5, -21.2)

Age			
< 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)
Race			
White	96/268 (35.8%)	90/147 (61.2%)	-25.9 (-35.6, -16.2)
Asian	18/35 (51.4%)	6/11 (54.5%)	-3.1 (-39.1, 32.9)
Black	1/5 (20.0%)	2/4 (50.0%)	NA
Other**	7/17 (41.2%)	5/8 (62.5%)	NA
Ethnicity			
Hispanic	12/24 (50.0%)	5/10 (50%)	0.0 (-41.1, 41.1)
Non-Hispanic	107/288 (37.2%)	95/154 (61.7%)	-25.4 (-34.8, -16.0)
Not-reported/unknown	3/13 (23.1%)	3/6 (50%)	NA

Source: ADSL and ADEFF datasets

* Confidence intervals taken from Applicant's analysis as presented in Tables 14.2-45 and 14.2-46 of P001V01 CSR

**Other race: 1 native Hawaiian/Pacific Islander in the letermovir arm; the remaining "others" represent subjects with multiple reported races.

Except for the Hispanic ethnicity subgroup, letermovir was favored in the primary efficacy endpoint analysis in all subgroups included in the table above. In the Hispanic subgroup, the rate of clinically significant CMV infection at Week 24 was exactly the same in both arms (50%). Notably, this is a relatively small subgroup. The rate of clinically significant CMV infection at Week 24 was *statistically significantly* lower in the letermovir arm for many subgroups. Exceptions to this were the age ≥ 65 years, Asian race, and Hispanic ethnicity. In each of the subgroups where the effect of letermovir failed to reach statistical significance, the sample size of the subpopulation was small. Also of note, the Black subgroup was too small to perform a meaningful subgroup analysis.

Reviewer Comment: The only subgroups in which the efficacy of letermovir has not clearly been demonstrated are in Hispanics and Blacks. Additional efficacy data from these populations in future postmarket trials will be of interest and may warrant a PMC.

7.1.4. Dose and Dose-Response: Trial P020

As described in Section 6.2.2, Trial P020 demonstrated a reduction in the rate of CMV prophylaxis failure that increased in magnitude with ascending letermovir doses. This reduction in CMV prophylaxis failure reached statistical significance with the two higher letermovir doses tested, but not with the lowest dose. This study nicely demonstrates letermovir's dose-dependent impact on CMV infection.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Both Trials P001 and P020 demonstrated a statistically significant reduction in CMV infection in the early post-transplant period (through Weeks 14 and 12 post-transplant in P001 and P020,

respectively). As discussed in Section 6.1.2, Trial P001 demonstrated that this reduction in CMV infection was maintained through Week 24 post-transplant (time of the primary efficacy endpoint assessment), despite discontinuation of letermovir at Week 14. No data are available for Trial P020 beyond Week 12.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no additional considerations on benefit in the postmarket setting to discuss in this section.

7.2.2. Other Relevant Benefits

In addition to preventing CMV infection and the morbidity and mortality that can result as a direct consequence of the virus, letermovir also prevents the use of toxic anti-CMV therapies. As described in Section 2.2, currently available anti-CMV agents are associated with significant toxicity, including bone-marrow toxicity which is particularly poorly tolerated in the HSCT population. In trial P001, the rate of decrease in leukocyte count (all grades) was numerically higher in the placebo arm (11.8% and 13.0% in the letermovir arm and placebo arms, respectively). Similarly, the rate of decrease in absolute neutrophil count (ANC) (all grades) was numerically higher in the placebo arm (12.4% and 14.1% in the letermovir and placebo arms, respectively). In Trial P020, the proportion of subjects with an on-treatment decrease in ANC of ≥ 20% was higher in the placebo arm than in any of the letermovir arms (24.4% in all letermovir arms combined compared to 30.3% in the placebo arm). Please see Section 8.4.6 for additional details on the laboratory findings in the clinical trials.

Reviewer Comment: This reviewer is somewhat surprised by the relatively similar rate of leukopenia and neutropenia in the placebo and treatment arm of Trial P001. In fact, although the rates of any grade abnormalities in leukocyte and neutrophil counts were higher in the placebo arm, the rate of Grade 4 decreases in leukocyte count was slightly higher in the letermovir arm and the rate of Grade 4 decreases in neutrophil counts was nearly identical in the two arms. Perhaps the use of growth factors in subjects experiencing on-treatment leukopenia and neutropenia accounted for the similar rates of events in both arms. This hypothesis is supported by the Applicant's finding that a larger proportion of placebo subjects compared to letermovir subjects in Trial P001 (37.0% and 33.5% of placebo and letermovir subjects, respectively) required the granulocyte colony stimulating factor filgrastim during the treatment window.

7.3. Integrated Assessment of Effectiveness

The efficacy of letermovir was primarily established in a single Phase 3 trial (P001) with support from a single Phase 2b trial (P020). Only the Phase 3 trial studied the to-be-marketed dose of

letermovir. There were 570 subjects treated in this trial and 495 subjects included in the efficacy population (325 of whom received letermovir). While the number of subjects in whom efficacy was demonstrated is small, for a drug that treats a relatively rare condition and has been granted both orphan drug status and breakthrough therapy designation, it is considered to be adequate. The small p-value and robust data from Trial P001 combined with supportive evidence of efficacy from Trial P020 provide confidence in the efficacy of letermovir for the prevention of CMV infection in HSCT recipients.

8 Review of Safety

8.1. Safety Review Approach

The pivotal Phase 3 Trial P001 and the supportive Phase 2b Trial P020 were analyzed individually. Safety findings from these two trials will be presented in detail in this review. Each of these major trials included a placebo arm allowing for optimal assessment of safety in a complex patient population with a high baseline rate of death, AEs, and laboratory abnormalities. Safety data from the Phase 2 and Phase 3 trials were not pooled because different doses were used in each of these trials. A Phase 2a Trial, P019, involved much lower doses and a shorter duration than the proposed dose and duration of letermovir for CMV prophylaxis. Further, in Trial P019 letermovir was administered for a (b) (4) and enrolled predominantly kidney transplant subjects. Therefore, safety data from Trial P019 is not relevant to the proposed indication and is not discussed in detail in this review. Lastly, the safety data from Phase 1 trials of letermovir were reviewed. However, the integrated summary of safety (ISS) databases allow for the assessment of safety across all Phase 1 trials but do not allow for an assessment by dose or duration of exposure. Therefore, only a limited, high-level discussion of the safety findings from the Phase 1 trials is included in this review.

Preclinical fertility and embryonic development toxicology studies showed nonreversible testicular degeneration and reduced fertility indices in rats (but not in monkeys) receiving high doses of letermovir. Therefore, potential testicular dysfunction was carefully assessed in our safety evaluation. Trial P001 involved the collection of serum inhibin B, LH, FSH, and testosterone levels at baseline, the end of treatment (i.e., 14 weeks post-transplant), and Week 24 post-transplant. These levels were analyzed, AEs pertaining to male fertility were evaluated, and the Division of Bone and Reproductive Urologic Products was consulted.

ADAM and SDTM datasets for Trial P001 and P020 were analyzed in JReview. Any differences in findings by the FDA reviewer compared to the Applicant were relatively minor and are unlikely to impact the overall assessment of the safety profile of letermovir. All of the safety

assessments and conclusions in this review are those of the FDA clinical reviewer unless otherwise specified.

As agreed upon at the pre-NDA meeting, the Applicant submitted a clinical study report (CSR) including Week 48 efficacy and safety data in lieu of the Safety Update Report (SUR) on June 8, 2017. This CSR contained cumulative safety results through Week 48. Although AEs occurring in the Week 24 to Week 48 period are less likely to be drug-related, the report and data were reviewed thoroughly and important findings were incorporated into the review that follows.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The exposure to oral and IV letermovir across Phase 1, 2, and 3 trials is summarized in the table below.

Table 20. Letermovir Safety Database

Clinical Trial Groups	Letermovir oral	Letermovir IV	Active Control	Placebo
Phase 1 trials[a]	538	142[d]	0	138
Controlled trials conducted for this indication[b]	465	99	0	225
Controlled trials conducted for (b) (4)	18	0	9	0
Total	1021	241	9[e]	363

[a]Includes healthy volunteers and subjects with renal or hepatic impairment
[b]Includes subjects from P001 (Phase 3) and P020 (Phase 2b)
[c]Includes subjects from P019 (Phase 2a) (b) (4) in SOT and HSCT recipients
[d]Includes 50 subjects who received only the original (b) (4) IV formulation. However, these 50 subjects were not included in the integrated Phase 1 safety analysis for IV letermovir (12 of these 50 subjects also received oral letermovir and they were included in the integrated safety analysis).
[e]Valganciclovir

Early in the development of IV letermovir, an (b) (4) formulation was used in two Phase 1 clinical trials (P017 and P018). Due to the occurrence of mild to moderate injection site reactions, the IV formulation was later changed to a hydroxypropyl betadex (hydroxypropyl beta-cyclodextrin HP β-CD) formulation. The numbers presented in Table 20 (in particular the 142 subjects who received IV letermovir in the Phase 1 program) include 50 subjects who

received the original (b) (4) formulation. Twelve of the subjects who received the (b) (4) IV formulation also received oral letermovir and were therefore included in the integrated Phase 1 safety analysis. However, the remaining 38 subjects who received only the (b) (4) IV letermovir formulation were not included in the integrated Phase 1 safety analysis. In total, 191 subjects are included in the IV letermovir safety database.

In total, 1157 subjects were exposed to IV and/or PO letermovir (the 12 subjects in Phase 1 trials and 93 subjects in the Phase 3 trial who received both IV and PO therapy are only counted once in this calculation). The letermovir doses administered in the Phase 1 and Phase 2 trials were often lower than the proposed dose. Additionally, the duration of letermovir administration was shorter than the proposed duration in many early trials. In total, 753 subjects received letermovir at doses equal to or higher than the proposed dose: 362 Phase 1 subjects (26 of whom received 240 mg + cyclosporine), 18 Phase 2b subjects enrolled in P020 (received 240 mg daily + cyclosporine), and 373 Phase 3 subjects enrolled in P001 (480 mg daily or 240 mg daily with cyclosporine). However, among these, only 391 subjects received letermovir for both the dose and duration as proposed in the label.

As noted above, a total of 191 subjects received the HP β-CD formulation of IV letermovir. The 92 subjects exposed in Phase 1 trials received short durations (up to 8 days) of doses ranging from 5 mg to 960 mg. Therefore, the safety database for IV letermovir comes primarily from Trial P001. The exposure to IV letermovir in Trial P001 is summarized below.

Table 21. P001: IV Letermovir Exposure (ASaT Population)

IV Letermovir Dose*	≥ 1 Dose (n)	≤ 2 Weeks (n)	> 2 Weeks – 4 Weeks (n)	> 4 Weeks (n)	Duration Range (Days)	Mean Duration (Days)
240 mg	37	23	11	3	1 - 45	13.6
480 mg	66	36	26	4	1 - 47	13.5

Source: P001v01 CSR (table 14.3-1)
*Subjects may have received both doses if cyclosporine was started or stopped during IV letermovir administration. Therefore, the total number of subjects who received one or more doses of IV letermovir is 99.

In Trial P001, 99 subjects received one or more dose of IV letermovir. Approximately 2/3rds of these subjects received the higher letermovir dose. The maximum duration of exposure was 47 days and the mean duration was nearly 14 days.

8.2.2. Relevant characteristics of the safety population:

As noted previously, the safety data from Trial P020 and P001 were not pooled for analysis as the two trials administered different doses of letermovir. Please see Section 6.1.2 and 6.2.2 for details regarding the demographic and baseline characteristics of the safety population for Trial

P001 and P020, respectively. Across both trials, Black and Hispanic patients were underrepresented. Additionally, the proportion of subjects who received a cord blood transplant and the proportion of subjects who received alemtuzumab were low. However, these findings reflect current HSCT practices. Cord blood transplantation is still a relatively new practice. Although utilization of cord blood stem cells is growing, it continues to make up a small portion of HSCTs. In 2012, commercial sale of alemtuzumab was terminated in the US and Europe. Although it is still available through a drug distribution program, use of alemtuzumab has since declined. Though the alemtuzumab and cord blood subgroups represent a small portion of HSCT recipients, they are notable as subgroups at increased risk for CMV infection. Other than these noted shortcomings, important subgroups appear well-represented within the letermovir safety population.

8.2.3. Adequacy of the safety database:

According to the draft CMV guidance, a safety database consisting of 300-500 subjects who received the recommended dose and duration (or longer) is recommended. Therefore, the overall safety database is considered to be adequate.

Reviewer Comment: It is not clear what size safety database is needed for individual formulations of a drug. The safety database for the IV letermovir formulation is relatively small. Given safety concerns that may be unique to the IV formulation (see Section 8.5.1 for details), additional safety data for the IV formulation are of interest.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no identified issues regarding data integrity. All narratives for deaths, related SAEs, related AEs leading to treatment discontinuation, events of clinical interest, and CMV disease events were reviewed carefully. There were minor errors in the submission (e.g. one death narrative listed the wrong subject ID number, laboratory values included in one subject's narrative belonged to a different subject) that were not felt to compromise the overall interpretation of the data. Additionally, rates of specific safety events as reported by the Applicant were verified by this reviewer (results were either identical to those of the Applicant or were off by only 1-2 subjects).

8.3.2. Categorization of Adverse Events

In the Phase 3 trial, P001, all AEs were collected through 14 days after completion of treatment period. Thereafter, only SAEs related to study medication or SAEs leading to death were collected through Week 48 post-transplant. All AEs were assigned a trial epoch/phase based on the day of onset: screening (time of informed consent through treatment initiation), treatment (time of initiation of study medication through 14 days following last dose of study medication),

primary follow-up (Week 16 through Week 24 post-transplant), secondary follow-up (Week 24 through Week 48 post-transplant), and post-study (after study completion or discontinuation).

In the Phase 2b trial, P020, all AEs were collected from the time the subject signed the informed consent through the last day of the trial (Day 92/7 days after therapy completed). Treatment-emergent AEs were defined as those AEs that started or worsened on or after initiation of trial medication and within 7 days after the last dose of trial medication.

There were no identified issues with respect to recording, coding, and categorizing AEs in either trial. The Applicant categorized SAEs in accordance with standard, regulatory definitions. However, the Applicant did not use a standard toxicity grading scale to categorize the severity of AEs in either trial, but instead used a mild, moderate, and severe grading scale. Below are the definitions used for Trial P001:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity
- Severe: incapacitating with inability to work or do usual activity

The severity categories were similarly defined in Trial P020.

8.3.3. Routine Clinical Tests

For Trial P001, routine clinical evaluation including AE assessment, CMV disease assessment, and CMV DNA PCR occurred weekly from Day 1 through Week 14, then every other week through Week 24, then at Weeks 32, 40, and 48. Safety laboratory tests were performed at Day 1, Weeks 2, 4, 8, 12, 14, 16, and at any CMV infection visit. Electrocardiograms (ECGs) were performed at screening, Week 2, and Week 14. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trial. The frequency and scope of this testing was considered adequate.

For Trial P020, routine clinical evaluation including AE assessment, CMV disease assessment, and CMV DNA PCR occurred on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 85, and 92. ECGs, physical examination, and safety laboratory testing occurred at pre-specified time points. The schedule of events was considered acceptable.

8.4. Safety Results

Trial P001

The table below displays an overview of treatment-emergent safety events through database lock for Trial P001. For this trial, 'treatment-emergent' was defined as an event occurring between the time of initiation of study drug and 14 days following the last dose of study drug.

The majority of subjects in both arms experienced at least 1 AE. A greater proportion of subjects in the letermovir arm had AEs that were assessed by the investigator as related to the study drug. Conversely, a greater proportion of subjects in the placebo arm experienced AEs that lead to treatment discontinuation. This increased rate of treatment discontinuation in the placebo arm was driven largely by subjects experiencing CMV reactivation and initiating preemptive CMV therapy. The rate of SAEs, drug-related SAEs, and discontinuations due to SAEs were all slightly higher in the placebo arm. The rate of treatment-emergent death was similar in the two arms.

Table 22. P001: Overview of Treatment-emergent Safety Events (ASaT Population)

	Letermovir 480 mg/day N=373	**Placebo N=192**
Adverse Events		
Any AEs	364 (97.6)	192 (100.0)
Drug-related AEs	63 (16.9)	23 (12.0)
Discontinuation due to AEs	71 (19.0)	98 (51.0)
Serious Adverse Events		
Any SAEs	163 (43.7)	90 (46.9)
Drug-Related SAEs	3 (0.8)	3 (1.6)
Discontinuation due to SAEs	34 (9.1)	27 (14.1)
Death	37 (9.9)	17 (8.9)

Source: AEPLUS dataset.
Presented as n (%)

Reviewer comment: The rates reported in the table above reflect the results obtained by this reviewer. This reviewer was unable to reproduce the rates reported in the CSR for the letermovir arm for many of these categories (e.g. the CSR reported 165 SAEs in the letermovir arm and 38 deaths in the letermovir arm). These discrepancies are small and are unlikely to impact the overall safety assessment.

Trial P020:

The table below provides an overview of safety events from the Phase 2b trial, P020. The doses used in this trial were lower than those used in the Phase 3 trial and lower than the proposed to-be-marketed dose (with the exception of a small subset of subjects in the letermovir 240 mg arm who were receiving concomitant cyclosporine). However, the use of three different letermovir arms and a placebo arm allows for assessment of potential dose-related safety trends. For this trial, 'treatment-emergent' was defined as events that started or worsened on or after initiation of study medication and within 7 days after the last dose of study medication.

Table 23. P020: Overview of Treatment-Emergent Safety Events (SS Population)

	Letermovir 60 mg/day N = 33	Letermovir 120 mg/day N = 31	Letermovir 240 mg/day N = 34	Placebo N = 33
Adverse Events				
Any AEs	31 (93.9)	29 (93.6)	34 (100.0)	33 (100.0)
Drug-related AEs	11 (33.3)	4 (12.9)	2 (5.9)	11 (33.3)
Discontinuation due to AEs	9 (27.3)	9 (29.0)	7 (20.6)	19 (57.6)
Serious Adverse Events				
Any SAEs	9 (27.3)	12 (38.7)	9 (26.5)	12 (36.4)
Drug-Related SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to SAEs	2 (6.1)	2 (6.5)	2 (5.9)	5 (15.2)
Death	2 (6.1)	0 (0.0)	1 (2.9)	1 (3.0)

Source: ADAE dataset
Presented as n (%)

Reviewer Comment: There does not appear to be a dose-dependent increase in the rate of events in any of the AE categories presented in the table above. Discontinuations due to AEs or SAEs were more frequent in the placebo arm than in any of the letermovir arms. As was observed in Trial P001, the majority of treatment discontinuations were due to CMV infection

8.4.1. Deaths

Trial P001

Through database lock there were a total of 123 deaths. The trial epoch in which the AE resulting in death began is presented below (see Section 6.1.1 for definitions of trial epochs). Of note, subjects may not have actually died in the same epoch in which the "fatal AE" began. Please see Section 6.1.2 for a presentation of time to mortality analyses. None of the AEs resulting in death were considered by the investigator to be treatment-related. In addition to assessing each death for relatedness to study drug, the investigators also assessed each death as being relapse or non-relapse related. Relapse refers to return of the condition for which transplantation was performed (e.g. relapse of AML). Accordingly, non-relapse mortality was defined by the Applicant as death due to any reason other than the primary condition for which the transplant was performed. A summary of all deaths (through database lock) in Trial P001, including the Applicant's assessment of study drug-relatedness and relapse-relatedness is provided in the table below.

Table 24. P001: Summary of Deaths through Database Lock (ASaT Population)

	Letermovir N = 373	Placebo N = 192	Total N = 565
Deaths	77 (20.6)	46 (24.0)	123 (21.8)

Epoch at onset of AE leading to death			
Screening	1(0.3)*	0 (0.0)	1 (0.2)
Treatment	37 (9.9)	17 (8.9)	54 (9.6)
Primary follow-up	23 (6.2)	21 (10.9)	44 (7.8)
Secondary follow-up	16 (4.3)	8 (4.2)	24 (4.2)
Post-study	0 (0)	1 (0.5)**	1 (0.2)
Treatment-related			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Relapse-related			
Yes	32 (8.6)	18 (9.4)	50 (8.8)

Source: ADAE and ADSL datasets. Analyses performed in JReview.
* AE onset was in screening period but death occurred in treatment period.
**AE onset occurred after study completion. This death (subject 0185-102197) was not included in Applicant's analysis of AEs associated with a fatal outcome (they report 122 deaths, 77 in the letermovir arm and 45 in the placebo arm).

Reviewer comment: After careful review of all provided narratives, this reviewer agrees that none of the deaths appear likely to have been related to the study drug. The cause of death in these subjects is complex and often multifactorial. A detailed description of all non-relapse deaths is provided in Appendix 13.2. Regarding the relapse and non-relapse related designations, it should be noted that there appears to be some inconsistency in reporting. Some investigators considered any death in a subject who had experienced relapse of the underlying condition that led to transplantation to be a relapse-related death. Other investigators assessed the cause of death to be a more proximal event (e.g. GVHD, infection), even if that event was likely a result of relapsed disease. However, as relapse-related mortality is considered an exploratory endpoint, this inconsistency is unlikely to impact the overall assessment of the efficacy of letermovir.

Non-Relapse Related Deaths

A large number of deaths in Trial P001 were considered to be relapse-related (41.6% of deaths in the letermovir arm and 39.1% of deaths in the placebo arm through database lock were relapse-related). These deaths were less-likely to have been impacted by the study drug. Therefore, while all narratives were reviewed, non-relapse deaths were evaluated more closely. Through database lock, in the ASaT population, there were 73 non-relapse – related deaths (45 (12.1%) in the letermovir arm and 28 (14.6%) in the placebo arm) and 50 relapse-related deaths (32 (8.6%) in the letermovir arm and 18 (9.4%) in the placebo arm). All non-relapse deaths are summarized in Appendix 13.2.

Reviewer's Comment: The majority of non-relapse deaths have an identifiable etiology, most commonly resulting directly or indirectly from infection or GVHD.

Treatment-Emergent Deaths

From a safety perspective, deaths due to events that started during the treatment window are

of greatest interest. The most common treatment-emergent AEs leading to death among the ASaT population are shown in the table below. The two most common fatal AEs (AML and GVHD) occurred with similar frequency in the letermovir and the placebo arms. When the PTs septic shock and sepsis are combined, the rate of fatal septic events is also similar in both arms (2.1% vs 1.6% in the letermovir and placebo arms, respectively). When looking at the System Organ Class level, as expected, the most common class of AEs leading to death was the Neoplasms benign, malignant and unspecified class. Fatal AEs from this class occurred numerically more often in the letermovir arm (4.8%) than the placebo arm (2.6%). The next most common System Organ Class was the Infections and infestations class. The rate of fatal infectious AEs was similar in the letermovir and placebo arms (2.4% and 3.1%, respectively). Rates of fatal AEs from other System Organ Classes were similarly low in both arms.

Table 25. P001: Fatal AEs with Treatment-Phase Onset Occurring in ≥ 2 Subjects

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Acute myeloid leukemia recurrent	7 (1.9%)	3 (1.6%)
Graft versus host disease	5 (1.3%)	3 (1.6%)
Septic shock	3 (0.8%)	3 (1.6%)
Sepsis	3 (0.8%)	1 (0.5%)
Acute myeloid leukemia	2 (0.5%)	1 (0.5%)
Venoocclusive liver disease	1 (0.3%)	2 (1.0%)
Acute lymphocytic leukemia recurrent	2 (0.5%)	0 (0.0%)
Bronchopulmonary aspergillosis	1 (0.3%)	1 (0.5%)
Pneumonia	2 (0.5%)	0 (0.0%)
Respiratory failure	2 (0.5%)	0 (0.0%)

Source: ADAE dataset

Reviewer comment: The common causes of death observed in this study are all events for which HSCT recipients are at increased risk. There do not appear to be any clinically meaningful imbalances in the types of AEs that result in death between the two arms.

Week 48 CSR Data

In total, there were 130 deaths reported in the final Week 48 CSR. One-hundred and twenty-three of these deaths were included in the original NDA submission and are therefore included in all of the above analyses and discussions. There were 7 new deaths (5 in the letermovir arm and 2 in the placebo arm) included in the Week 48 CSR. None of these additional deaths were considered by the investigator to be related to study drug. The narratives for each of these additional deaths were reviewed carefully and are briefly summarized below.

- 003-102116 (letermovir): Subject developed recurrent mantle cell lymphoma on Day 154 and died due to disease progression on Day 358. Of note, subject withdrew from

the study on Day 186.

- 0091-102193 (letermovir): Subject had CAC confirmed gastrointestinal CMV end-organ disease, diagnosed on Day 140 and resolved on Day 183. On Day 373, subject experienced a cerebrovascular accident and died the same day. Of note, this AE began after week 48 and this subject is therefore not included in the Applicant's analysis of AEs that lead to fatal outcomes.
- 0161-100348 (letermovir): The subject was diagnosed with relapsed AML on Day 241 and died AML on Day 250.
- 0108-102065 (letermovir): On Day 66 the subject was diagnosed with relapsed myelodysplastic syndrome. The subject died of the relapsed disease on Day 463.
- 0164-102040 (letermovir): The subject developed a fever and respiratory failure on Day 291. The subject decompensated rapidly and died on Day 292.
- 0091-100122 (placebo): The subject developed recurrent AML on Day 114. Despite receiving various salvage regimens, the subject died of AML on Day 449.
- 0164-102258 (placebo): This subject was diagnosed with sepsis on Day 260 and was found to have a multi-drug resistant organism in blood cultures. Subject died of sepsis on Day 261.

Reviewer Comment: These deaths are similar in nature to those included in the original CSR. Four of the seven newly reported deaths were due to relapse of the underlying disease leading to transplantation. Two of the three remaining deaths (one in each arm) appear attributable to infection, which is a known, common complication following HSCT. Lastly, the details surrounding the death due to a cerebrovascular accident are unclear. It is not known if it was a hemorrhagic or thrombotic stroke and no laboratory values are reported for this timeframe. Regardless, oncology patients are at risk for both bleeding and thrombotic events. These deaths do not impact the overall safety profile of letermovir.

In addition to the new deaths reported in the Week 48 CSR, the death narrative for subject 0005-101927 was modified and the AE resulting in death was changed from ALL to pneumothorax.

Reviewer Comment: It is unclear what prompted the change in the cause of death for subject 0005-101927. However, the re-categorization of a single death from relapse to non-relapse does not meaningfully impact the study results.

Trial P020

There were 4 deaths due to treatment-emergent AEs in Trial P020; 2 in the letermovir 60 mg/day arm, 1 in the letermovir 240 mg/day arm, and 1 in the placebo arm. These deaths are briefly described below.

- Subject 108002 (letermovir 60 mg/day): Subject died from gastrointestinal GVHD on Day 59. Of note, GVHD was first reported on Day 21 at which time the study medication was

discontinued. Subject also had pneumonia around the time of death. The death was not thought to be due to study drug.

- Subject 201002 (letermovir 60 mg/day): This subject experienced AML relapse on Day 91 and died from the relapse on Day 109. He also experienced pneumonia and respiratory failure around the time of death. The subject's last dose of study medication was on Day 84. This death was not thought to be due to study drug.
- Subject 101015 (letermovir 240 mg/day): A pneumonia SAE was reported on Day 28. The infection progressed leading to multi-organ failure and ultimately death on Day 37. The subject continued study drug up until Day 36. The death was not thought to be related to the study drug.
- Subject 206005 (placebo): This subject died of bacterial pneumonia that began on Day 14 and led to death on Day 24. The death was not thought to be related to the study drug.

Reviewer comment: It is notable that all 4 subjects experiencing fatal AEs in Trial P020 had pneumonia around the time of death, even if pneumonia was not considered to be the cause of death. HSCT recipients are known to be at high risk for infectious complications such as pneumonia, as evidenced by the fact that the single death in the placebo arm was also due to pneumonia. When looking at the larger Phase 3 trial data, there were two subjects in the letermovir arm and none in the placebo arm whose cause of death was pneumonia. Pneumonia SAEs were slightly more common in the letermovir arm compared to the placebo arm in both Trial P020 and Trial P001; however, the numbers are small overall. In conclusion, this reviewer agrees that the deaths in Trial P020 are unlikely to be due to the study drug.

8.4.2. Serious Adverse Events

Trial P001

There were a total of 253 subjects who experienced treatment-emergent SAEs, 163 of which were in the letermovir arm and 90 were in the placebo arm. All SAEs occurring in 3 or more subjects in the letermovir arm, regardless of causality, are presented in the table below. Overall, the type and rate of SAEs was similar in the letermovir and placebo arms. CMV infection and acute kidney injury SAEs were more common in the placebo arm. No specific SAEs were notably more common in the letermovir arm, although pneumonia was reported in a slightly higher proportion of subjects in the letermovir arm than in the placebo arm.

Table 26. P001: Treatment-Emergent SAEs Occurring in at Least 3 Letermovir Subjects

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Graft versus host disease	37 (9.9%)	20 (10.4%)

Acute myeloid leukemia recurrent	11 (3.0%)	7 (3.7%)
Cytomegalovirus infection	10 (2.7%)	13 (6.8%)
Pneumonia	8 (2.1%)	3 (1.6%)
Pyrexia	7 (1.9%)	4 (2.1%)
Acute kidney injury	5 (1.3%)	9 (4.7%)
Sepsis	5 (1.3%)	2 (1.0%)
Febrile neutropenia	5 (1.3%)	2 (1.0%)
Septic shock	4 (1.1%)	5 (2.6%)
Acute myeloid leukemia	4 (1.1%)	2 (1.0%)
Urinary tract infection	4 (1.1%)	0 (0.0%)
Respiratory failure	4 (1.1%)	0 (0.0%)
Staphylococcal bacteremia	3 (0.8%)	2 (1.0%)
Transplant failure	3 (0.8%)	2 (1.0%)
Thrombocytopenia	3 (0.8%)	1 (0.5%)
Vomiting	3 (0.8%)	1 (0.5%)
Bronchopulmonary aspergillosis	3 (0.8%)	1 (0.5%)
Clostridium difficile colitis	3 (0.8%)	1 (0.5%)
Epstein-Barr virus infection	3 (0.8%)	0 (0.0%)
Headache	3 (0.8%)	0 (0.0%)
Acute lymphocytic leukemia recurrent	3 (0.8%)	0 (0.0%)
Venoocclusive disease	3 (0.8%)	0 (0.0%)
Squamous cell carcinoma	3 (0.8%)	0 (0.0%)
Sinusitis	3 (0.8%)	0 (0.0%)

Source: ADAE dataset

Reviewer comment: It is plausible that the increased rate of acute kidney injury observed in the placebo arm is partially attributable to the use of nephrotoxic agents for the treatment of CMV infection. However, an analysis of creatinine laboratory values reported during the treatment period may provide a more accurate assessment of renal function, as laboratory values were routinely measured and consistently reported. Please see Section 8.4.6 for a summary of treatment-emergent changes in serum creatinine values.

Among the reported SAEs, only 6 were considered by the investigator to be study drug-related (3 in the letermovir arm and 3 in the placebo arm). Narratives were provided for each of these treatment-related SAEs and are summarized below.

- **0020-101650 (letermovir)**: This is a 39 year-old female with chronic myeloid leukemia. She first experienced a thrombocytopenia AE on the day prior to randomization (platelet count = 129 x 10^9/L, normal range 150 – 400 x 10^9/L). On Day 1, her platelet count was 92,000/mm^3 (normal range 130,000-400,000/mm^3). She received multiple transfusions as well as other treatments for possible immune thrombocytopenic purpura (tranexamic acid, intravenous immunoglobulin, plasmapheresis, rituximab, and romiplostim) throughout the course of the study. Despite this, her thrombocytopenia persisted. She

experienced several mild, non-serious bleeding AEs (rectal hemorrhage, mouth hemorrhage, epistaxis, and angina bullosa hemorrhagica). On Day 81, with a platelet count of 4,000/mm^3, thrombocytopenia was classified as an SAE on the basis of being life-threatening and the study drug was permanently discontinued. Of note, the thrombocytopenia did not necessitate or prolong a hospitalization. Her platelet count slowly increased after the study drug was discontinued.

- **0100-100116 (letermovir)**: This is a 50 year-old male with a history of myelodysplastic syndrome. On Day 49 he experienced an SAE of pancytopenia, for which he was hospitalized. At baseline, the subject had thrombocytopenia and anemia which were relatively stable throughout treatment. However, the subject's WBC count and ANC were normal at baseline and had a peak on-treatment toxicity grade of 4. The pancytopenia was assessed by the investigator to be treatment related and study drug was discontinued on Day 50. By Day 60, his hematologic parameters had increased only minimally. On Day 64 he experienced a second SAE, cellulitis, for which he was admitted to the ICU. Then on Day 96 he experienced an SAE of gastrointestinal hemorrhage, which ultimately led to his death on Day 124. The events cellulitis and gastrointestinal hemorrhage were not considered to be treatment related. At time of death, the subject's pancytopenia was ongoing.
- **0116-100454 (letermovir)**: This is a 45 year-old male with a history of angiocentric lymphoma who underwent cord blood transplantation. On study Day 10 (post-transplant Day 21), the SAE delayed engraftment, was reported and the study medication was discontinued. Subsequently, his hematologic laboratory parameters slowly increased and on study Day 19 he was considered to have engrafted. The delayed engraftment was assessed by the investigator to be related to the study drug. The subject experienced CMV viremia after letermovir had been discontinued and after engraftment had occurred (CMV DNA first detectable on Day 50).
- **0116-100452 (placebo):** This is a 61 year-old female with a history of AML. On Day 12, she experienced an SAE of mental status change. The event was described as unresponsiveness to stimuli occurring 5 minutes after infusion of the study drug. A head CT was performed and was unremarkable. The study drug was permanently discontinued that same day. She then went on to experience an SAE of subarachnoid hemorrhage on Day 57 after falling on Day 56. She was noted to have thrombocytopenia throughout the study, with a platelet count of 24,000 cells/µL around the time of the intracranial hemorrhage. She later experienced an SAE of mucormycosis of the sinuses on Day 96 and AML relapse on Day 106. Shortly thereafter, she transitioned to home hospice care. The investigator assessed the event of mental status change to be related to the study drug and all other events were assessed to be unrelated to study drug.
- **0146-101651 (placebo)**: This is a 56 year-old white male with a history of AML. On Day 21, he was diagnosed with Bowen's disease (squamous cell carcinoma in situ). This SAE was assessed by the investigator to be related to study drug and study drug was

permanently discontinued on Day 22. On Day 260, the subject experienced a second SAE, recurrent AML, which was not considered related to study drug. The subject ultimately died on Day 284 due to recurrent AML.

- **0013-100404 (placebo):** This is a 63 year-old male with a history of diffuse large B-cell lymphoma. On Day 3, he developed acute kidney injury and was hospitalized. The investigator assessed the event as due to study drug (reported that study drug may have caused elevated tacrolimus levels which in turn led to kidney injury). Tacrolimus was discontinued on Day 3, the study drug was discontinued on Day 5, and the subject was withdrawn from the study on Day 6. By Day 9, the AE was resolved.

Reviewer comment: This reviewer agrees that the above described SAEs may have been study drug related, with the following exceptions/caveats:

- *0116-100454 (delayed engraftment). There are several different definitions of delayed engraftment described in the literature. Most often, the term delayed engraftment described subjects who have failed to achieve engraftment at 14 – 28 days post-transplantation. At the time the diagnosis of delayed engraftment was made and the study drug was discontinued, the subject was only 21 days post-transplant. There are many factors that can contribute to delayed engraftment. Notably, cord blood transplantation is a known risk factor for delayed engraftment. This reviewer believes that this diagnosis may have been made prematurely. If the diagnosis of delayed engraftment is accepted, the case is confounded by the receipt of a cord blood transplant.*
- *0146-101651 (Bowen's disease): This reviewer believes there is insufficient evidence of causality. Primary risk factors for the development of Bowen's disease are sun exposure and aging and it seems unlikely that less than three weeks of exposure to any drug could impact the development of this pre-cancerous condition.*

During the primary follow-up period (between Week 16 and Week 24), the proportion of subjects experiencing SAEs remained higher in the placebo arm (22.9% vs 17.2% in the placebo and letermovir arms, respectively. None of these SAEs were assessed by the investigator to be drug-related. As seen in the treatment period, the four most commonly reported SAE PTs during the primary follow-up period were GVHD, recurrent AML, pneumonia, and CMV infection. GVHD was the most common SAE, however, while GVHD occurred in each arm at a similar rate during the treatment period, during the primary follow-up period GVHD was notably more common in the placebo arm (5.2% vs 1.9% in the placebo and letermovir arms, respectively). Serious CMV-related events (combining CMV infection and CMV viremia PTs) were uncommon, but slightly more prevalent in the letermovir arm (1.3% vs 0.5% in the letermovir arm and placebo arm, respectively). Pneumonia also remained more common in the letermovir arm (1.6% vs 0.5% in the letermovir and placebo arms, respectively).

<u>48 Week CSR Data</u>

Incomplete data regarding SAEs occurring during the secondary follow-up period (between Week 24 and 48) were included in the original NDA submission due to the timing of the database lock. The 48 Week CSR contained complete SAE data through Week 48. The overall proportion of subjects with SAEs through Week 48 remained higher in the placebo arm (59.9%) than the letermovir arm (53.6%). None of the SAEs occurring between Week 24 and Week 48 were assessed by the investigator to be treatment related. Therefore, no additional SAE narratives (except for those SAEs that resulted in death) were included in the 48 Week CSR. Analysis of the cumulative SAEs through Week 48 (including the treatment, primary follow-up, and secondary follow-up period) revealed that the most commonly reported PTs were GVHD, recurrent AML, CMV infection, and pneumonia. Each of these events was more common in the placebo arm, except for pneumonia which was numerically slightly more common in the letermovir arm, but essentially comparable in both arms (4.0% vs 3.1% in the letermovir arm and placebo arm, respectively).

Reviewer Comment: Through Week 48, the SAEs reported are generally reflective of the types of complications HSCT recipients are at risk for in this post-transplant period (GVHD, disease recurrence, and infection).

Trial P020:

The most common treatment-emergent SAEs occurring in Trial P020 are presented in the table below. Acute GVHD and pneumonia both occurred slightly more frequently among subjects receiving letermovir compared to placebo.

Table 27. P020: Treatment Emergent SAEs Occurring in ≥ 2 Subjects in Any Arm

Preferred Term	Letermovir 60 mg N = 33	Letermovir 120 mg N = 31	Letermovir 240 mg N = 34	Letermovir All N = 98	Placebo N = 33
Acute GVHD, intestine	2 (6.1%)	0 (0.0%)	2 (5.9%)	4 (4.1%)	5 (3.0%)
Pneumonia	1 (3.0%)	1 (3.2%)	2 (5.9%)	4 (4.1%)	4 (2.4%)
CMV infection	0 (0.0%)	1 (3.2%)	0 (0.0%)	1 (1.0%)	3 (1.8%)
Pyrexia	1 (3.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	3 (1.8%)
Febrile neutropenia	0 (0.0%)	1 (3.2%)	0 (0.0%)	1 (1.0%)	2 (1.2%)
AML	1 (3.0%)	1 (3.2%)	0 (0.0%)	2 (2.0%)	2 (1.2%)
Pneumonia primary atypical	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (1.0%)	2 (1.2%)
EBV infection	1 (3.0%)	0 (0.0%)	1 (2.9%)	2 (2.0%)	2 (1.2%)
Leukemia recurrent	1 (3.0%)	0 (0.0%)	1 (2.9%)	2 (2.0%)	2 (1.2%)

Source: ADAE dataset

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Trial P001

AEs led to treatment discontinuation in 71 (19%) subjects in the letermovir arm and 98 (51%)

subjects in the placebo arm. AEs commonly associated with treatment discontinuation are presented in the table below. The most common reason for treatment discontinuation in both arms was CMV infection leading to the initiation of preemptive CMV therapy. Treatment discontinuations due to CMV infection occurred more commonly in the placebo arm than in the letermovir arm (39% vs 6%, respectively). Excluding the subjects who discontinued treatment due to CMV Infection, the rate of treatment discontinuations due to AEs was similar in the placebo and treatment arms (12% and 13%, respectively). Other than CMV infection, no specific AEs led to treatment discontinuation more commonly in one arm than in the other arm.

Table 28. P001: AEs Leading to Treatment Discontinuation in ≥ 2 Subjects in Either Arm

Preferred Term	**Letermovir N=373 N (%)**	**Placebo N=192 N (%)**
Cytomegalovirus infection	23 (6.2%)	75 (39.1%)
Nausea	6 (1.6%)	2 (1.0%)
Acute myeloid leukemia recurrent	4 (1.1%)	1 (0.5%)
Graft versus host disease	3 (0.8%)	2 (1.0%)
Vomiting	3 (0.8%)	0 (0.0%)
Venoocclusive liver disease	2 (0.5%)	2 (1.0%)
Blood creatinine increased	2 (0.5%)	1 (0.5%)
Abdominal pain	2 (0.5%)	0 (0.0%)
Pneumonia	2 (0.5%)	0 (0.0%)
Septic shock	1 (0.3%)	2 (1.0%)

Among subjects experiencing AEs that led to treatment discontinuation, 18 (4.8%) and 7 (3.7%) subjects in the letermovir and placebo arms, respectively, had AEs that were assessed by the investigator to be treatment-related. The most common AEs considered by the investigator to be related to the study drug that led to treatment discontinuation were nausea, vomiting, and abdominal pain.

Trial P020

AEs led to treatment discontinuation in 25.5% of subjects in the letermovir arms and 57.6% of subjects in the placebo arm. As was observed in Trial P001, the majority of treatment discontinuations were due to CMV infection. All other AEs that led to treatment discontinuations occurred in no more than 2 letermovir or placebo subjects and were similar to the events leading to discontinuation in Trial P001.

8.4.4. Significant Adverse Events

Trial P001

As described previously, the Applicant categorized AEs as mild, moderate, or severe in intensity. A comparison of severe treatment-emergent AEs between arms is presented in the table below. Severe pyrexia, thrombocytopenia, mucosal inflammation, and sepsis occurred more commonly in the letermovir arm, although the differences are small. Further discussion regarding thrombocytopenia can be found in Section 8.4.6.

Table 29. P001: Severe AEs in ≥ 5 Subjects in Either Arm, Irrespective of Causality

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Graft versus host disease	36 (9.7%)	16 (8.3%)
Acute myeloid leukemia recurrent	9 (2.4%)	7 (3.6%)
Cytomegalovirus infection	8 (2.1%)	8 (4.2%)
Acute kidney injury	5 (1.3%)	8 (4.2%)
Pyrexia	**10 (2.7%)**	**2 (1.0%)**
Thrombocytopenia	**9 (2.4%)**	**2 (1.0%)**
Febrile neutropenia	6 (1.6%)	4 (2.1%)
Pneumonia	**7 (1.9%)**	**3 (1.6%)**
Platelet count decreased	5 (1.3%)	4 (2.1%)
Septic shock	4 (1.1%)	5 (2.6%)
Hepatic function abnormal	5 (1.3%)	3 (1.6%)
Mucosal inflammation	**7 (1.9%)**	**0 (0.0%)**
Sepsis	**5 (1.3%)**	**2 (1.0%)**

Source: AEPLUS dataset

Trial P020

As in Trial P001, severity of AEs in Trial P020 was categorized as mild, moderate or severe. The majority of treatment emergent AEs were of mild or moderate severity. Across all letermovir arms, 23/98 (23.5%) subjects experienced severe treatment-emergent AEs, compared to 10/33 (30.3%) in the placebo arm. The rates of specific events were similarly low in both arms, and no individual PT was reported in more than 2 letermovir subjects.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Trial P001:

Most (97.6%) subjects treated with letermovir experienced one or more treatment-emergent AEs and all (100.0%) subjects treated with placebo experienced a treatment-emergent AE. Irrespective of causality and severity, the most common AEs reported in both arms were GVHD, nausea, diarrhea, pyrexia, and rash. Most of the common AEs occurred with similar frequency in both arms. AEs that occurred at least 2% more frequently in the letermovir arm include

nausea, vomiting, edema peripheral, cough, headache, fatigue and abdominal pain. See the table below for additional details regarding common treatment-emergent AEs in Trial P001.

Table 30. P001: Treatment-Emergent Adverse Events occuring in ≥ 10% of Letermovir Subjects, All Severity and Irrespective of Causality

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Graft versus host disease	146 (39.1%)	73 (38.0%)
Nausea	**99 (26.5%)**	**45 (23.4%)**
Diarrhea	97 (26.0%)	47 (24.5%)
Pyrexia	77 (20.6%)	43 (22.4%)
Rash	76 (20.4%)	41 (21.4%)
Vomiting	**69 (18.5%)**	**26 (13.5%)**
Edema peripheral	**54 (14.5%)**	**18 (9.4%)**
Cough	**53 (14.2%)**	**20 (10.4%)**
Headache	**52 (13.9%)**	**18 (9.4%)**
Fatigue	**50 (13.4%)**	**21 (10.9%)**
Mucosal inflammation	46 (12.3%)	23 (12.0%)
Abdominal pain	**44 (11.8%)**	**18 (9.4%)**

Source: AEPLUS dataset

Reviewer Comment: All events bolded in the table above occurred more frequently in the letermovir arm than the placebo arm. In a placebo-controlled study, the observation that an event occurs more often in the study drug arm than the placebo arm can be used as a marker of causality. It should be noted that with multiple comparisons, any numerical differences may be chance occurrences and the findings should therefore be interpreted cautiously. Nonetheless, this reviewer considers this method of assigning causality to be more meaningful than relying on investigator assessments of causality, which are subject to variability and subjectivity. Therefore, these events should be included in Section 6 of the label as adverse events.

Using the MedDRA-based Adverse Event Diagnostics (MAED) program, the following less common (< 10%) PTs appear to have been reported significantly more often in the letermovir arm:

- Myalgia (5.1% letermovir vs. 1.6% placebo; 3.5% risk difference (95% CI: 0.7, 6.4))
- Hyperkalemia (7.2% letermovir vs. 2.1% placebo; 5.2% risk difference (95% CI: 1.8, 8.5))
- Dyspnea (8.0% letermovir vs. 3.1% placebo; 4.9% risk difference (95% CI: 1.2, 8.6))

Several PTs were reported more often in the placebo arm (CMV infection, gastroesophageal reflux disease, ageusia, pharyngeal inflammation, post-transplant lymphoproliferative disorder, dehydration, myopathy, presyncope, and abdominal pain upper). It is important to note that the confidence intervals provided above are not corrected for multiple comparisons and are for exploratory purposes only.

Reviewer comment: The significance of the increased rate of myalgia, hyperkalemia, and dyspnea reported in the letermovir arm is unclear. The fact that there was such a large number of PTs that occurred more often in the placebo arm suggests that many of these apparent differences between arms may be due to chance. Of note, the rate of treatment-emergent potassium laboratory abnormalities (reported in the ADLB dataset) was similar in both arms and this is generally considered to be a more reliable method of assessing laboratory abnormalities (see Section 8.4.6 below).

When analyzed at the SOC level, gastrointestinal AEs were the most commonly observed AEs in the letermovir arm and infection AEs were the most commonly observed AEs in the placebo arm, as shown in the following table.

Table 31. P001: Treatment Emergent AEs by SOC

System Organ Class	Letermovir N=373 N (%)	Placebo N=192 N (%)
Gastrointestinal disorders	261 (70.0%)	129 (67.2%)
Infections and infestations	241 (64.6%)	139 (72.4%)
General disorders and administration site conditions	210 (56.3%)	99 (51.6%)
Skin and subcutaneous tissue disorders	178 (47.7%)	80 (41.7%)
Immune system disorders	153 (41.0%)	79 (41.1%)
Respiratory, thoracic and mediastinal disorders	147 (39.4%)	71 (37.0%)
Nervous system disorders	137 (36.7%)	64 (33.3%)
Metabolism and nutrition disorders	134 (35.9%)	63 (32.8%)
Investigations	133 (35.7%)	58 (30.2%)
Musculoskeletal and connective tissue disorders	121 (32.4%)	57 (29.7%)
Blood and lymphatic system disorders	97 (26.0%)	51 (26.6%)
Renal and urinary disorders	81 (21.7%)	46 (24.0%)
Vascular disorders	69 (18.5%)	40 (20.8%)
Psychiatric disorders	78 (20.9%)	30 (15.6%)
Eye disorders	62 (16.6%)	32 (16.7%)
Injury, poisoning and procedural complications	42 (11.3%)	27 (14.1%)
Cardiac disorders	47 (12.6%)	12 (6.3%)
Neoplasms benign, malignant and unspecified	39 (10.5%)	17 (8.9%)
Reproductive system and breast disorders	30 (8.0%)	11 (5.7%)
Hepatobiliary disorders	22 (5.9%)	15 (7.8%)
Ear and labyrinth disorders	17 (4.6%)	2 (1.0%)
Endocrine disorders	6 (1.6%)	0 (0.0%)
Congenital, familial and genetic disorders	2 (0.5%)	1 (0.5%)

Source: AEPLUS dataset

The higher rate of infection AEs in the placebo arm appears to arise from the increased rate of CMV infection occurring in the placebo arm. If the PTs pertaining to CMV infection (cytomegalovirus infection and cytomegalovirus viremia) are excluded, the number of subjects in the letermovir arm and placebo arm with one or more AEs in the Infection and Infestation SOC is actually higher in the letermovir arm (59.5% and 48.4%, respectively). See Section 8.5.4 for a more detailed analysis of infection AEs.

There was a numerically higher rate of events in the letermovir arm compared to the placebo arm for several SOCs (see table above). This higher rate of events was assessed to be potentially significant for the cardiac disorders SOC (6.4% risk difference [95% CI: 1.6, 11.2]) and the ear and labyrinth disorders SOC (3.5% difference [95% CI: 1.0, 6.1]). These risk differences were calculated using the MAED program and as stated previously, the reported confidence intervals are for exploratory purposes only. The Applicant conducted a post-hoc safety analysis that included cardiac events and ear and labyrinth events. An in-depth discussion of each of these potential safety signals is presented in Section 8.5.

All AEs were assessed by the investigator to be either related or not related to study drug. The table below presents the most common related treatment-emergent events in P001. Elsewhere in this review and in labeling, related adverse events may be described as adverse reactions. The overall rate of treatment-emergent, related AEs was higher in the letermovir arm (16.9% and 12.0% in the letermovir and placebo arms, respectively). Nausea, diarrhea, and vomiting were the most common AEs to be considered treatment-related and they all occurred more frequently in the letermovir arm.

Table 32. P001: Related Treatment-Emergent AEs occurring in ≥ 3 Letermovir Subjects

Preferred Term	**Letermovir N=373 N (%)**	**Placebo N=192 N (%)**
Nausea	27 (7.2%)	7 (3.7%)
Diarrhea	9 (2.4%)	2 (1.0%)
Vomiting	7 (1.9%)	2 (1.0%)
Alanine aminotransferase increased	3 (0.8%)	2 (1.0%)
Blood creatinine increased	3 (0.8%)	1 (0.5%)
Abdominal pain	3 (0.8%)	1 (0.5%)
Muscle spasms	3 (0.8%)	0 (0.0%)

Source: AEPLUS dataset

The majority of the safety analyses performed for Trial P001 looked at events occurring in the treatment phase (from the start of study medication through 14 days after the last dose of study medication). However, as toxicity associated with chemotherapy generally peaks 7-10 days after HSCT and is typically resolved by 30 days after HSCT, we conducted additional

analyses of safety focusing on this early post-transplant period. Analyses looking at events occurring within 30 days of transplantation as well as events occurring during the first 30 days of study drug exposure were conducted. The rate of events observed in the early post-transplant period was generally lower than the rate observed over the entire treatment period (likely due to shorter period of time over which AEs were assessed). The type and severity of events as well as the distribution of events across treatment arms was not markedly different in the early post-transplant period compared to the entire treatment period.

Reviewer comment: This latter finding is reassuring and suggests that letermovir does not enhance chemotherapy-associated toxicity in the early post-transplant period.

Trial P020

Across all arms, the majority of subjects in Trial P020 experienced one or more AE (94/98, 96.0% in the letermovir arms and 33/33, 100.0% in the placebo arm). The most common treatment-emergent AEs are presented in the table below. Overall, the type and frequency of events observed in this trial are similar to those in Trial P001. Two notable exceptions are the lower reported rates of GVHD in all arms of Trial P020 and the higher rate of CMV infection in all letermovir arms in Trial P020 (perhaps due to suboptimal letermovir dosing). AEs that showed a potential dose-related increase in frequency include headache, edema peripheral, diarrhea, pyrexia, decreased appetite, pruritus, and acute skin GVHD. The markedly higher rate of cough in the letermovir arms compared to the placebo arm is also noteworthy.

Table 33. P020: Treatment-Emergent Adverse Events Occurring in ≥ 10% of Subjects Letermovir Arms, All Severity and Irrespective of Causality

Preferred Term	Letermovir 60 mg N = 33	Letermovir 120 mg N = 31	Letermovir 240 mg N = 34	Letermovir All N = 98	Placebo N = 33
Diarrhea	9 (27.3%)	9 (29.0%)	11 (32.4%)	29 (29.6%)	10 (30.3%)
Nausea	7 (21.2%)	8 (25.8%)	7 (20.6%)	22 (22.4%)	11 (33.3%)
Vomiting	4 (12.1%)	10 (32.3%)	8 (23.5%)	22 (22.4%)	4 (12.1%)
CMV infection	6 (18.2%)	6 (19.4%)	5 (14.7%)	17 (17.3%)	11 (33.3%)
Fatigue	3 (9.1%)	8 (25.8%)	4 (11.8%)	15 (15.3%)	5 (15.2%)
Headache	4 (12.1%)	3 (9.7%)	8 (23.5%)	15 (15.3%)	3 (9.1%)
Edema peripheral	4 (12.1%)	3 (9.7%)	8 (23.5%)	15 (15.3%)	3 (9.1%)
Cough	2 (6.1%)	8 (25.8%)	5 (14.7%)	15 (15.3%)	1 (3.0%)
Acute GVHD in skin	3 (9.1%)	5 (16.1%)	6 (17.6%)	14 (14.3%)	2 (6.1%)
Rash	4 (12.1%)	5 (16.1%)	4 (11.8%)	13 (13.3%)	6 (18.2%)
Renal failure	5 (15.2%)	5 (16.1%)	3 (8.8%)	13 (13.3%)	2 (6.1%)
Pyrexia	3 (9.1%)	4 (12.9%)	5 (14.7%)	12 (12.2%)	6 (18.2%)
Decreased appetite	4 (12.1%)	2 (6.5%)	5 (14.7%)	11 (11.2%)	3 (9.1%)
Pruritus	2 (6.1%)	4 (12.9%)	5 (14.7%)	11 (11.2%)	3 (9.1%)

Insomnia	5 (15.2%)	4 (12.9%)	2 (5.9%)	11 (11.2%)	0 (0.0%)
Constipation	4 (12.1%)	3 (9.7%)	3 (8.8%)	10 (10.2%)	1 (3.0%)

Source: ADAE dataset

Reviewer Comment: Assessing dose-dependent safety signals in Trial P020 is challenging given the small numbers of subjects in each arm. Overall, the AEs are similar to what was observed in Trial P001. See section 8.11 for an integrated assessment of safety findings from Trials P001 and P020.

AEs in Trial P020 were assessed by investigators as being not related, unlikely related, possibly related, probably related, or definitely related. No AEs were assessed as being definitely related. For this review, the relationship categories not related and unlikely related are combined, and the categories possibly and probably related are combined. Possibly and probably related AEs that occurred in 2 or more letermovir subjects are presented in the table below.

Table 34. P020: Common Related AEs

Preferred Term	Letermovir 60 mg N = 33	Letermovir 120 mg N = 31	Letermovir 240 mg N = 34	Placebo N = 33
Diarrhea	4 (2.4%)	0 (0.0%)	1 (0.6%)	2 (1.2%)
Vomiting	3 (1.8%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
ALT increased	1 (0.6%)	0 (0.0%)	2 (1.2%)	1 (0.6%)
AST increased	2 (1.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Headache	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Dyspepsia	0 (0.0%)	1 (0.6%)	1 (0.6%)	1 (0.6%)
Rash	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Transaminases	0 (0.0%)	2 (1.2%)	0 (0.0%)	0 (0.0%)
Myalgia	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Blood alkaline phosphatase increased	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Edema peripheral	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: ADAE dataset

The most commonly reported AEs that were potentially related to study drug were diarrhea, vomiting, ALT increase, and AST increase. None of these common related AEs demonstrated a dose-dependent increase. In fact, diarrhea, vomiting, and AST increased PTs were all most commonly reported in the lowest letermovir dose cohort.

8.4.6. Laboratory Findings

Trial P001

The following two tables display treatment-emergent, graded laboratory abnormalities for chemistry and hematology parameters in P001. These analyses present the worst change from baseline per subject. Subjects who had abnormal results for the same laboratory test on more than one occasion are counted only once at the highest toxicity grade. The Division of AIDS (DAIDS) version 2.0 scale for grading the severity of adverse events was used to grade laboratory abnormalities. Of note, the Applicant used different denominators for the laboratory toxicity grade calculations than those shown in the tables below. Their denominator for the letermovir arm was 371 and for the placebo arm was 191. This appears to be due to the Applicant excluding 2 subjects from the letermovir arm and one from the placebo arm that did not have any post-baseline lab results. This discrepancy does not impact the overall laboratory findings.

Table 35. P001: Treatment-Emergent Abnormalities* in Key Chemistry Parameters by Highest Toxicity Grade

Laboratory Parameter	Letermovir N=373 N (%)	Placebo N=192 N (%)
Alanine Aminotransferase (IU/L)		
Grade 1 (1.25 to <2.5 x ULN)	42 (11.3)	23 (12.0)
Grade 2 (2.5 to <5.0 x ULN)	14 (3.8)	16 (8.3)
Grade 3 (5.0 to <10.0 x ULN)	7 (1.9)	3 (1.6)
Grade 4 (≥10.0 x ULN)	6 (1.6)	0 (0.0)
Any Grade	69 (18.5)	42 (21.9)
Alkaline Phosphatase (IU/L)		
Grade 1 (1.25 to <2.5 x ULN)	37 (9.9)	15 (7.8)
Grade 2 (2.5 to <5.0 x ULN)	10 (2.7)	8 (4.2)
Grade 3 (5.0 to <10.0 x ULN)	2 (0.5)	0 (0.0)
Any Grade	49 (13.1)	23 (12.0)
Aspartate Aminotransferase (IU/L)		
Grade 1 (1.25 to <2.5 x ULN)	31 (8.3)	26 (13.5)
Grade 2 (2.5 to <5.0 x ULN)	11 (3.0)	9 (4.7)
Grade 3 (5.0 to <10.0 x ULN)	6 (1.6)	2 (1.0)
Grade 4 (≥10.0 x ULN)	2 (0.5)	0 (0.0)
Any Grade	50 (13.4)	37 (19.3)
Bilirubin, Total (mg/dL)		
Grade 1 (1.1 to <1.6 x ULN)	19 (5.1)	9 (4.7)
Grade 2 (1.6 to <2.6 x ULN)	10 (2.7)	3 (1.6)
Grade 3 (2.6 to <5.0 x ULN)	4 (1.1)	4 (2.1)
Grade 4 (≥5.0 x ULN)	6 (1.6)	5 (2.6)
Any Grade	39 (10.5)	21 (10.9)
Creatinine (mg/dL)		
Grade 1 (1.1 to 1.3 x ULN)	4 (1.1)	0 (0.0)

Laboratory Parameter	Letermovir N=373 N (%)	Placebo N=192 N (%)
Grade 2 (>1.3 to 1.8 x ULN or increase of >0.3 mg/dL above baseline)	43 (11.4)	17 (8.8)
Grade 3 (>1.8 to <3.5 x ULN or increase of 1.5 to <2.0 x baseline)	102 (27.1)	55 (28.4)
Grade 4 (≥3.5 x ULN or increase of ≥2.0 x baseline)	75 (19.9)	31 (16.0)
Any Grade	224 (60.1)	103 (53.6)
Potassium (mmol/L)		
Grade 1 (5.6 to < 6.0)	4 (1.1)	6 (3.1)
Grade 2 (6.0 to < 6.5)	3 (0.8)	0 (0.0)
Grade 3 (6.5 to < 7.0)	0 (0.0)	1 (0.5)
Any Grade	7 (1.9)	7 (3.6)

Source: ADLB dataset
* The abnormality refers to an elevation above the upper limit of normal

As shown in the table above, Grade 3 and 4 elevations in ALT and AST were uncommon but slightly more prevalent in the letermovir arm. Combining all Grades, ALT and AST elevations were more common in the placebo arm. Grade 3 and 4 bilirubin elevations were also uncommon overall, but were more common in the placebo arm. Potential Hy's Law cases are discussed in detail in Section 8.5.6.

Creatinine elevations were common, occurring in more than half of the subjects in each arm. Any Grade creatinine elevations and Grade 4 elevations were more common in the letermovir arm. According to an analysis performed by the Applicant, among subjects with a treatment-emergent Grade 3 or 4 creatinine abnormality, 45.8% of letermovir subjects and 51.2% of placebo subjects had returned to their baseline creatinine by Week 16. Regarding renal AEs, there were more subjects experiencing treatment-emergent AEs under the renal SOC in the placebo arm than in the letermovir arm (24.0% vs 21.7%, respectively). Serious renal AEs were uncommon, but were also more prevalent in the placebo arm (5.7% vs 2.7% in the placebo and letermovir arms, respectively). Analysis of the acute renal failure MAED SMQ suggests that acute renal failure events occurred with similar frequency in the placebo and letermovir arms (21.9% and 21.7%, respectively).

Reviewer comment: The significance and etiology of the observed increased rate of creatinine elevation in the letermovir arm compared to the placebo arm is unclear. In preclinical studies, the kidney was not a target organ for toxicity. It is conceivable that the finding is due to nephrotoxicity associated with the β-cyclodextrin contained in the IV formulation of letermovir. However, analysis of the maximum creatinine toxicity grades among subjects who received IV therapy compared to those who did not (see Section 8.5.1), does not support this theory. The higher rate of overall renal AEs and SAEs in the placebo arm and the balance of acute renal

failure events across the arms are reassuring. Nonetheless, this higher proportion of subjects with increased creatinine levels in the letermovir arm compared to the placebo arm should be included in the label.

Analysis of electrolyte parameters revealed no major safety concerns. As previously noted, the AE hyperkalemia was reported more often in the letermovir arm. However, in the ADLB dataset, potassium elevation was uncommon overall and the rate of Grade 1-3 potassium elevation was similar in both arms. There were no Grade 4 potassium elevations. Analysis of calcium levels revealed that Grade 1 and 2 hypocalcemia was common in both arms (23.5% and 23.6% in the letermovir and placebo arms, respectively). Grade 3 hypocalcemia occurred in 3.5% of the letermovir arm and 2.6% of the placebo arm. Grade 4 hypocalcemia occurred in ≤ 1% of both arms. Hypercalcemia was uncommon in both arms, with only a single Grade 3 abnormality reported in the letermovir arm and no hypercalcemia events of any grade in the placebo arm.

Treatment-emergent hematologic laboratory abnormalities are of particular interest in the HSCT population. Cytopenias are common and drugs to be used in this population should ideally not exacerbate or prolong bone marrow suppression. As noted previously, bone marrow suppression is the primary toxicity that limits the utility of the currently available anti-CMV drugs, ganciclovir and valganciclovir, in this population.

Table 36. P001: Treatment-Emergent Abnormalities* in Key Hematology Parameters by Highest Toxicity Grade

Laboratory Parameter	Letermovir N=372 N (%)	Placebo N=192 N (%)
Hemoglobin (g/dL)		
Grade 1 (10.0 to 10.9 (Male) / 9.5 to 10.4 (Female))	20 (5.3%)	5 (2.6%)
Grade 2 (9.0 to <10.0 (Male) / 8.5 to <9.5 (Female))	43 (11.4%)	18 (9.3%)
Grade 3 (7.0 to <9.0 (Male) / 6.5 to <8.5 (Female))	78 (20.7%)	33 (17.0%)
Grade 4 (<7.0 (Male) / <6.5 (Female))	8 (2.1%)	6 (3.1%)
Any Grade	149 (40.1%)	62 (32.3%)
Leukocytes (10^3/µL)		
Grade 1 (2.0 to 2.499)	10 (2.7%)	11 (5.7%)
Grade 2 (1.5 to 1.999)	5 (1.3%)	1 (0.5%)
Grade 3 (1.0 to 1.499)	8 (2.1%)	4 (2.1%)
Grade 4 (<1.0)	21 (5.6%)	9 (4.6%)
Any Grade	44 (11.8%)	25 (13.0%)
Absolute neutrophil count (10^3/µL)		
Grade 1 (0.8 to 1.0)	3 (0.8%)	3 (1.6%)

Grade 2 (0.6 to 0.799)	5(1.3%)	6 (3.1%)
Grade 3 (0.4 to 0.599)	11 (3.0%)	4 (2.1%)
Grade 4 (<0.4)	27 (7.2%)	14 (7.3%)
Any Grade	46 (12.4%)	27 (14.1%)
Platelet (10^3/µL)		
Grade 1 (100 to <124.999)	8 (2.1%)	3 (1.5%)
Grade 2 (50 to <100)	12 (3.2%)	11 (5.7%)
Grade 3 (25 to <50)	20 (5.3%)	8 (4.1%)
Grade 4 (<25)	50 (13.3%)	19 (9.8%)
Any Grade	90 (24.2%)	41 (21.4%)

Source: ADLB dataset
* The abnormality refers to an elevation above the upper limit of normal

Overall, it appears that the rate and severity of treatment-emergent hematologic abnormalities is relatively comparable in the two arms. There is an increase in hemoglobin toxicity in the letermovir arm that is driven primarily by Grade 1, 2, and 3 abnormalities; and an increase in platelet toxicity in the letermovir arm that is driven primarily by Grade 4 abnormalities.

Reviewer comment: It is difficult to interpret the hematologic laboratory abnormalities given the high rate of baseline hematologic toxicity in this patient population and the many confounding factors. The findings presented in the table above suggest that letermovir is not associated with an increase in WBC and ANC abnormalities compared to placebo. This is an important improvement over currently marketed anti-CMV drugs. Comparatively, as reported in the IV ganciclovir label, among HSCT recipients receiving IV ganciclovir pre-emptive therapy, 12% of subjects had an ANC < 500/µL and 29% had an ANC of 500 – 1000/ µL in comparison with 6% and 17% of subjects receiving placebo who had an ANC < 500/ µL and 500 – 1000/ µL, respectively. However, there is a higher frequency of graded hemoglobin and platelet decreases among subjects receiving letermovir. It is unclear if these observed differences represent true differences in the population. This reviewer favors making these data available to prescribers in Section 6 of the package insert.

Because of the observed increased rate of Grade 4 thrombocytopenia in the letermovir arm, a careful analysis of bleeding events was undertaken. Bleeding PTs are dispersed across many body system organ classes. Therefore, the hemorrhages narrow standardized MedDRA query (SMQ) in MAED was used for this analysis. The SMQ revealed that the rate of hemorrhagic AEs was similar in both arms (20.9% and 20.8% in the letermovir and placebo arms, respectively). The most commonly reported hemorrhagic AEs were epistaxis, angina bullosa hemorrhagica, conjunctival hemorrhage, hematuria, contusion, petechia, hemoptysis, and hematoma. Serious hemorrhagic events were uncommon in both arms (2.7% and 3.1% in the placebo and letermovir arms, respectively). The specific types and rates of serious hemorrhagic AEs are shown in the table below. In addition to the serious bleeding events listed in the table, a

subject in the letermovir arm (0131-101954) experienced a fatal AE of thrombocytopenia. This subject is not included in the 50 letermovir subjects with treatment emergent Grade 4 thrombocytopenia as this subject had Grade 4 thrombocytopenia at baseline secondary to myelodysplastic syndrome. This subject had persistent thrombocytopenia, leading to study drug discontinuation on Day 9. He subsequently developed respiratory and renal failure and died following a cardiac arrest on Day 11. The investigator cited thrombocytopenia as the cause of death, though there is no description of a bleeding event and it is not clear how thrombocytopenia led to organ failure in the absence of bleeding.

Table 37. P001: Serious Treatment-Emergent Bleeding Events

Event Grouping	Letermovir N=373 N (%)	Placebo N=192 N (%)
Intracranial hemorrhage	3 (0.8%)	2 (1.0%)
Gastrointestinal hemorrhage	3 (0.8%)	0 (0.0%)
Cystitis/hematuria	2 (0.5%)	2 (1.0%)
DIC	1 (0.3%)	0 (0.0%)
Other*	1 (0.3%)	2 (1.0%)

Source: MAED analysis
*Other = stomatitis hemorrhagic (letermovir), Immune thrombocytopenia purpura (placebo), and uterine hemorrhage (placebo)

The 69 subjects (50 letermovir and 19 placebo) with Grade 4 thrombocytopenia were assessed for bleeding events. Only 3 of these subjects (all in the letermovir arm) experienced on-treatment serious bleeding AEs. The reported events in these subjects included stomatitis hemorrhagic, gastrointestinal hemorrhage, and lower gastrointestinal bleed. Of note, at the time of the serious bleeding event, none of the subjects had Grade 4 thrombocytopenia. Two subjects had Grade 3 thrombocytopenia and 1 subject had Grade 2 thrombocytopenia at the time of hemorrhage.

Reviewer comment: Severe thrombocytopenia is common following stem cell transplantation. Platelet count along with platelet function, coagulation system function, and overall clinical condition all contribute to a subject's risk for hemorrhagic events. Generally, a platelet count of 10,000 to 20,000/µL is used a cut-off for prophylactic platelet transfusions. However, as the subjects in this study have demonstrated, bleeding events can occur at higher platelet counts. Given that the overall rate of thrombocytopenia was similar in both arms when all grades were combined (24.2% in the letermovir arm and 21.4% in the placebo arm) and given the similar rate of serious and non-serious bleeding events in the two arms, the clinical significance of the higher rate of Grade 4 thrombocytopenia in the letermovir arm is of unclear significance. However, inclusion of the platelet abnormalities observed in Trial P001 in the letermovir package insert is

recommended.
Given that potential hematologic toxicity is of particular interest, in addition to looking at the worst grade hematologic results, trends in hematologic parameters over time were also assessed. Graphs depicting the mean and standard deviation of platelet count, total WBC count, absolute neutrophil count, and hemoglobin level over time by arm were created. An example of these graphs is shown in the figure below, which depicts platelet count over time. For each of the hematologic parameters assessed, the trends over time were similar in the letermovir and placebo arm.

Figure 3. P001: Mean ± SD of Platelet Count Over Time

Source: ADLB dataset, figure created in JReview
Abbreviations: EOT, end of treatment; LOTTR, last observed time point

Trial P020

Abnormal laboratory results in Trial P020 were not graded for severity. Instead, the Applicant characterized laboratory results as below normal, normal, or above normal. The Applicant's laboratory analysis included an assessment of the number of subjects experiencing a shift from baseline to the lowest or highest post-baseline value using these categorical parameters (e.g., the number of subjects in each arm who went from low to normal, low to high, normal to high). There were no apparent differences in the rate of shifts in key laboratory parameters between

arms and no apparent dose-dependent trends in reported shifts within the 3 letermovir arms.

In addition to analyzing shifts in laboratory results, the Sponsor created "predefined change abnormals" (PCAs) for key laboratory parameters. For example, the PCA for hemoglobin was a decrease from baseline of ≥ 2 g/dL. For key laboratory parameters, the proportion of subjects with at least 1 predefined change was compared between arms (see table below). Overall, there were no clear trends in the rate of PCAs between arms. However, the higher rate of subjects meeting the platelet PCA in the highest dose letermovir arm compared to the lower dose letermovir arms and the placebo arm is notable, particularly in light of the increased rate of Grade 4 thrombocytopenia in the letermovir arm in Trial P001. Additionally, more subjects in the letermovir 60 mg/day arm and the letermovir 240 mg/day arm had a creatinine PCA compared to the letermovir arm. However, the letermovir 120 mg/day arm had the lowest rate of creatinine PCAs, so there was not a clear dose relationship.

Table 38. P020: Applicant's Analysis of Laboratory Abnormalities; Summary of Incidence of Predefined Changes

	Letermovir 60 mg/day N=33	Letermovir 120 mg/day N=31	Letermovir 240 mg/day N=34	Placebo N=33
Occurrence of at least 1 PC post-baseline:				
Hemoglobin (PC = -2 g/dL)	10 (30.3)	11 (35.5)	8 (23.5)	7 (21.2)
WBC (PC = -2000/mm^3)	11 (33.3)	13 (41.9)	10 (29.4)	9 (27.3)
Eosinophils (PC = +20%)	2 (6.1)	1 (3.2)	1 (2.9)	2 (6.1)
Neutrophils (PC = -20%)	9 (27.3)	9 (29.0)	6 (17.6)	10 (30.3)
Platelet count (PC = -100,000/mm^3)	4 (12.1)	0	6 (17.6)	4 (12.1)
ALT (PC = >2 ULN)	5 (15.2)	7 (22.6)	7 (20.6)	6 (18.2)
AST (PC = >2 ULN)	3 (9.1)	5 (16.1)	4 (11.8)	3 (9.1)
Creatinine (PC = >0.3 ULN)	15 (45.5)	13 (41.9)	17 (50.0)	14 (42.4)
Total bilirubin (PC = >0.5 ULN)	5 (15.2)	3 (9.7)	3 (8.8)	5 (15.2)
ALT (PC = ≤2-fold increase over ULN)	19 (57.6)	16 (51.6)	18 (52.9)	19 (57.6)
AST (PC = ≤2-fold increase over ULN)	16 (48.5)	14 (45.2)	14 (41.2)	19 (57.6)
ALT (PC = >2-3 ULN)	3 (9.1)	4 (12.9)	4 (11.8)	3 (9.1)
AST (PC = >2-3 ULN)	1 (3.0)	3 (9.7)	1 (2.9)	2 (6.1)
ALT (PC = >3-5 ULN)	1 (3.0)	2 (6.5)	2 (5.9)	5 (15.2)
AST (PC = >3-5 ULN)	1 (3.0)	2 (6.5)	2 (5.9)	2 (6.1)
ALT (PC = >5 ULN)	2 (6.1)	4 (12.9)	3 (8.8)	3 (9.1)
AST (PC = >5 ULN)	1 (3.0)	2 (6.5)	1 (2.9)	1 (3.0)

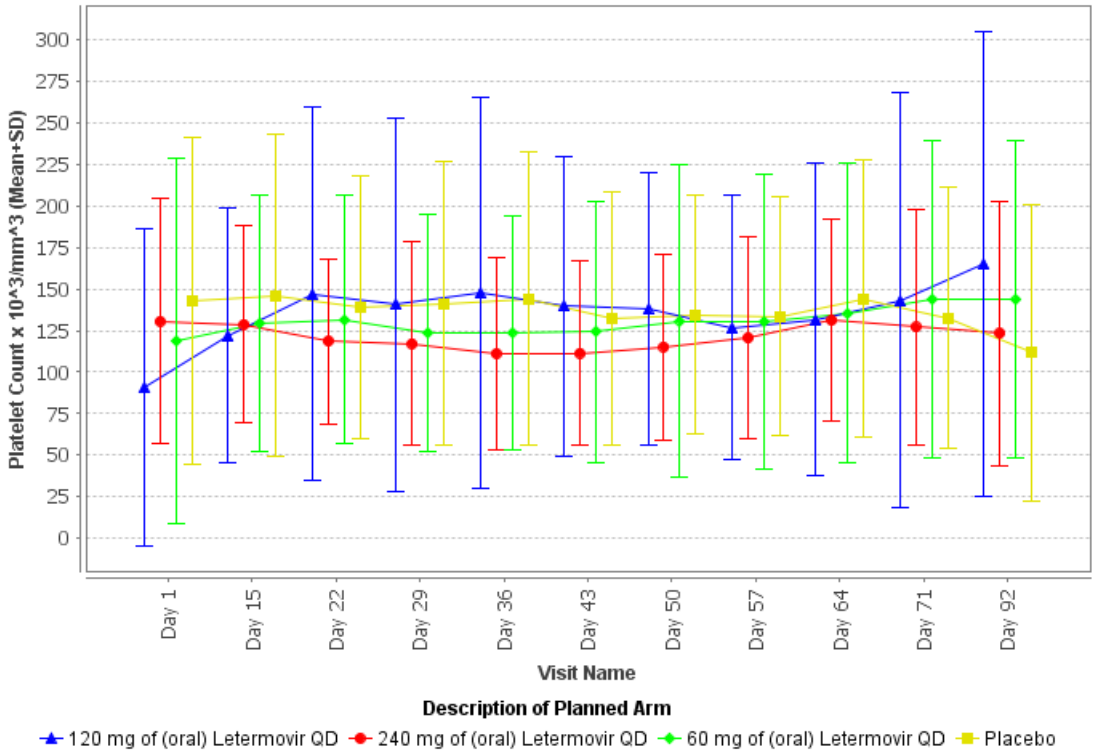
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; PC = predefined change; ULN = upper limit of normal; WBC = white blood cell.
Note: Predefined clinically significant laboratory values were defined as those with an increase or decrease from baseline equal to or greater than a predefined amount to an abnormal value (with the follow-up value outside the extended normal range). A PC could be an increase from a high to an even higher value or a decrease from a low value to an even lower value. The signs "-"and "+" denote the direction of predefined change (- decrease or + increase).
Source: Table 5.5.

Source: Applicant's P001 CSR

Reviewer comment: The figures in the table above suggest that large (i.e. > 100,000/mm^3) on-treatment decreases in platelets may be more common in subjects receiving higher doses of letermovir. However, this type of analysis only tells part of the story. On Day 1, 68/131 (51.9%) of subjects had a platelet count below 100,000/mm^3, meaning that a decrease of >100,000/mm^3 from baseline was not possible. To better describe platelet counts over time, the following figure was created. This figure shows that platelet counts in the letermovir 240 mg/day arm may have been lower than platelet counts in the other arms (particularly lower than the placebo arm) early on in the treatment period. However, by the end of the study these

differences were less pronounced.

Figure 4. P020: Median Platelet Count Over Time



Source: LB dataset. Figure created in JReview.

8.4.7. Vital Signs

In both Trial P001 and P020, heart rate, blood pressure, respiratory rate, and body temperature were measured at each on-treatment study visit and at the last visit. The mean change from baseline was relatively consistent across letermovir and placebo arms. No clinically meaningful changes in vital signs were observed in association with letermovir use.

8.4.8. Electrocardiograms (ECGs)

Trial P001

ECGs were performed at Screening, Week 2, and at the End of Study visit. On-treatment increases in the corrected QT interval (QTc) from baseline occurred at a similar frequency in both arms. Using the Fridericia formula, the mean change from baseline to Week 2 and end of treatment are presented in the table below. As shown, the mean post-baseline QTc intervals and the mean change in QTc interval are similar across arms.

Table 39. P001: Mean Change in Fridericia QTc Interval from Baseline*

Time Point and Treatment Arm	N	Mean (SD) QTc Interval (ms)	Mean (SD) Change from Baseline QTc Interval (ms)
Week 2			
Letermovir	282	417 (23.2)	0.5(22.3)
Placebo	147	417.5 (22.7)	0.7 (23.3)
End of Treatment			
Letermovir	318	413.4 (24.0)	- 2.0 (25.9)
Placebo	160	414.5 (22.1)	-2.2 (22.8)

Source: ADEG dataset
* Only the 318 letermovir subjects and 160 placebo subjects with baseline ECGs available are included

In addition, 46 (12.3%) subjects in the letermovir arm and 23 (12.0%) subjects in the placebo arm experienced an increase in QTc of > 30 ms from baseline. Marked QTc prolongation was uncommon in both the letermovir and placebo arm. An increase in QTc from baseline of > 60 ms was reported in 3 and 2 subjects in the letermovir and placebo arms, respectively. Only a single subject experienced a treatment-emergent QTc > 500 ms and this subject was in the placebo arm (QTc = 514 ms at week 12, QTc = 450 ms at Day 1). An additional 8 (2.1%) and 3 (1.6%) subjects in the letermovir and placebo arms, respectively, developed a QTc > 480 ms but ≤ 500 ms.

There were 4 subjects (all in the letermovir arm) with a reported AE of QT prolonged. Each of these events was considered mild or moderate in severity. The maximum QTc interval in these 4 cases was 402, 425, 475, and 476 ms. Three of these cases had clear risk factors for QT prolongation (cardiac conditions or use of QT prolonging medications). The only case without a clear risk factor was the case with a maximum QTc of 402 ms. In addition, one subject who experienced an on-treatment increase in QTc was reported to have experienced an AE of torsade de pointes (subject 0020-00018, see details below).

- **0020-100029 (letermovir)**: This was a 53 year-old female with a history of ALL and no cardiac history. She had a baseline QTc of 442 ms and a peak QTc of 491 at Week 2. On Day 35 she experienced an AE of torsade de pointes, graded as mild by the investigator. No QTc values are reported at the time of the torsade de pointes event (no ECGs available beyond Week 2). The most recent available laboratory results were from Day 27. At that time, she was mildly hypokalemic (potassium = 3.4 mmol/L, normal range is 3.5 – 5.3 mmol/L). No magnesium results were available. The torsade de pointes event was not discussed in the narrative. However, it appears that she was quite ill at the time of the event with renal failure, respiratory failure, and hypotension requiring the use of multiple vasopressors (including norepinephrine and vasopressin, both of which are associated with cardiac arrhythmias). Also of note, she experienced atrial fibrillation during the treatment period, for which she received several days of amiodarone

(associated with torsade de pointes) approximately 1 week prior to the occurrence of torsade de pointes. Lastly, she received domperidone, which has also been associated with QT prolongation. She ultimately died on Day 45 of bilateral fungal pneumonia. Both the torsade de pointes and the pneumonia were assessed by the investigator to be unrelated to the study drug.

There were no notable differences in the other ECG parameters between the letermovir and treatment arms.

Trial P020

Twelve-lead ECGs were routinely performed on Day 1, Day 8 or 15, and Day 92. All ECGs underwent automated analysis and manual analysis. The results described in this review are based on the manual reading of the ECGs by an expert(s) unless stated otherwise.

Marked increases in QTc from baseline (> 60 ms) were uncommon overall, occurring in 3 (3.1%) letermovir subjects and no placebo subjects. Similarly, markedly prolonged QTc values (> 480 ms) were uncommon, observed in one letermovir subject and no placebo subjects. The subject with an on-treatment QTc > 480 ms had a baseline QTc of 477 ms. According to the automated reading of the ECGs, there was a single subject with a QTc > 500 ms (in the letermovir arm), but this finding was not confirmed upon manual reading of the ECGs. Of note, these extreme changes in QTc results did not appear to be dose-related as two of the three subjects who experienced a > 60 ms increase in QTc from baseline were in the 60 mg/day letermovir cohort and the other was in the 120 mg/day letermovir cohort. No other notable ECG findings were reported.

Of note, the following treatment-emergent AEs regarding cardiac conduction were reported in a single subject each: sinus arrhythmia (placebo), QT prolonged (letermovir 60 mg/day), and ST segment elevation (letermovir 240 mg/day). Additionally, 3 subjects in the letermovir 120 mg/day cohort experienced tachycardia.

Reviewer Comment: Letermovir was not associated with meaningful ECG changes in the Phase 2b or Phase 3 clinical trials or in the thorough QT study (see Section 8.4.9).

8.4.9. **QT**

The Applicant conducted a thorough QT/QTc study (MK-8228-004) in which 33 healthy, female subjects received the following single-dose treatments in a randomized order: 1) 960 mg IV letermovir; 2) 480 mg IV letermovir; 3) placebo IV; and 4) 400 mg oral moxifloxacin.

A QT-IRT consult was requested and the review was submitted on June 1, 2017. The reviewer concluded that letermovir was not associated with significant QTc prolongation in this TQT

study. The largest upper bounds of the 2-sided 90% CI for the mean differences between letermovir (single dose of 480 mg IV and 960 mg IV) and placebo were below 10 ms, the threshold for regulatory concern. Further, the exposure achieved with the 960 mg IV dose used in this study was thought to "reasonably cover the highest clinically relevant concentrations with the intended therapeutic dosing of letermovir" and the moxifloxacin control established the assay sensitivity, as intended.

8.4.10. Immunogenicity

As letermovir is a small molecule, there is limited concern regarding the potential for immunogenicity. There was no evidence of immunogenicity or immunotoxicity in preclinical repeat-dose studies. Studies assessing the formation of anti-drug antibodies were not indicated for letermovir.

8.5. Analysis of Submission-Specific Safety Issues

On the basis of preclinical data and findings in standard safety analyses performed in Section 8.4, several potential submission-specific safety issues were identified. These issues are discussed in further detail in this section.

8.5.1. Intravenous Administration

In the Phase 3 trial, P001, the Applicant observed that among subjects not receiving cyclosporine, letermovir exposure was approximately 3-fold higher following administration of IV therapy compared to oral therapy. Therefore, careful investigation of the safety profile of IV letermovir and thoughtful consideration regarding the acceptability of the safety database for IV letermovir are necessary.

In Phase 1 trials, 142 subjects received IV letermovir, of whom, 92 received the to-be-marketed HP β-CD IV formulation. The safety profile observed among subjects receiving the HP β-CD IV letermovir formulation was similar to the safety profile observed in the overall letermovir population. There were no SAEs among Phase 1 subjects who received IV letermovir. No subjects in Phase 2 trials received IV letermovir.

In the Phase 3 trial, a total of 99 subjects received at least one dose of the IV formulation of letermovir. Among these, 72 subjects received 7 or more consecutive days of IV letermovir. The table below provides an overall summary of safety for the subset of subjects who received at least 7 consecutive days of IV therapy. Of note, although the overall trial was randomized 2:1 to the letermovir and placebo arms, respectively, among the subset of subjects who received 7 or more consecutive days of IV therapy the ratio of subjects who received IV letermovir to those who received IV placebo was closer to 3:1.

Reviewer Comment: It is not clear why a greater proportion of subjects in the letermovir arm than in the placebo arm received 7 or more days of IV therapy. Potential reasons for the use of IV therapy include an inability to take medications by mouth due to mucositis, significant gastrointestinal symptoms, and high acuity of illness (i.e. vasopressor use, ventilator dependency, etc.). Perhaps subjects in the letermovir arm experienced a greater number of these impediments than the placebo arm by chance. Alternatively, perhaps the increased proportion of subjects receiving IV therapy in the letermovir arm is attributable to the higher rate of nausea, vomiting, and diarrhea associated with oral letermovir than oral placebo (as evidenced in Section 8.4.5), which may have prompted a switch to IV therapy.

Table 40. P001: Overview of Safety Events Occurring During IV Therapy in Subjects Receiving ≥ 7 Consecutive Days of IV Therapy

	IV Letermovir N=72 N (%)	IV Placebo N=27 N (%)
Adverse Events		
Any AEs	63 (87.5)	24 (88.9)
Drug-related AEs	5 (6.9)	1 (3.7)
Discontinuation due to AEs	3 (4.2)	6 (22.2)
Serious Adverse Events		
Any SAEs	11 (15.3)	9 (33.3)
Drug-Related SAEs	0 (0.0)	1 (3.7)
Discontinuation due to SAEs	3 (4.2)	3 (11.1)
Death*	2 (2.8)	1 (3.7)

Source: ADAE dataset
*AE that resulted in death was treatment-emergent, but death may not have occurred until follow-up period.

Discontinuations due to AEs were more common in the IV placebo arm than in the IV letermovir arm. As with the overall population, the high rate of treatment discontinuation seen in the placebo arm was driven largely by discontinuations due to CMV infection. Additionally, AEs in the IV letermovir arm were more likely to be drug-related (as assessed by the investigator) compared to AEs in the placebo arm. The following 6 drug-related AEs were reported among 5 letermovir subjects during the period of IV administration: diarrhea, infusion site erythema, infusion site inflammation, nausea, prothrombin time prolonged, and renal impairment (each PT reported only once).

Reviewer Comment: The observed higher frequency of drug-related AEs in the letermovir arm was not unique to the subset of subjects receiving IV therapy (see Section 8.4.5).

SAEs and deaths associated with IV letermovir administration

When analyzing the entire treatment period (oral and IV letermovir or placebo), the rate of SAEs was markedly higher among subjects who had received 7 or more days of IV letermovir

compared to the letermovir population as a whole (46/72, 63.9% in the subset of subjects who received ≥ 7 days of IV letermovir compared to 163/373, 43.7% for the entire letermovir arm). However, this is not unexpected as subjects who required IV therapy were likely sicker than those who were able to take oral therapy. Therefore, any comparison of events among subjects who did and did not require 7 or more consecutive days of IV therapy must be interpreted cautiously. A comparison of placebo subjects who received 7 or more consecutive days of IV therapy vs. the placebo arm as a whole reveals similar findings (18/27, 66.7% in those who received ≥ 7 days of IV placebo compared to 90/192, 46.9% for the entire placebo arm).

SAEs occurring in more than one subject during IV therapy included GVHD (3 subjects in the letermovir arm and 1 in the placebo arm), respiratory failure (2 subjects in the letermovir arm and none in the placebo arm), and mucosal inflammation (2 in the letermovir arm and none in the placebo arm). It was noted that two subjects in the letermovir arm and 1 subject in the placebo arm experienced serious hepatic AEs during receipt of therapy. While the rate of hepatic events did not differ between arms, one case was noteworthy and is described below.

- 0116-102241 (letermovir): This was a 70 year-old woman with AML and no reported history of liver disease. She received IV letermovir on Days 1-15 and then on Day 16 was switched to oral letermovir. On Day 4 of IV letermovir treatment, she experienced an SAE of hyperbilirubinemia. Then on Day 10, an SAE of hepatic cirrhosis was reported. This event was associated with portal hypertension, abdominal pain, and generalized edema. She ultimately underwent paracentesis on Day 17, but no results were provided. On Day 18 she was reported to experience an SAE of encephalopathy. It was noted that she received morphine that day, but it is not clear if her altered mental status was attributable to pain medication, hepatic encephalopathy, or something else. A CT of the brain was unremarkable. However, on Day 22 her study medication was discontinued due to worsening encephalopathy. Review of her laboratory results showed that her bilirubin peaked at 4.2 mg/dL (normal range 0.2 – 1.3 mg/dL) on Day 14. ALT, AST, and alkaline phosphatase levels all remained within the normal range. Her INR was only mildly elevated (peaked at 1.7 on Day 1, the upper limit of normal is 1.1). Her albumin level was normal throughout the study. On Day 39 she was reported to have failure to thrive, which ultimately led to her death on Day 54. No autopsy was performed. None of these events were assessed by the investigator to be treatment related.

Reviewer comment: It is not clear based on the information provided that this subject truly developed cirrhosis. There were potential confounding factors for the modestly elevated bilirubin (e.g. voriconazole use from day -7 to -2 and Day -1 to 19, methotrexate use from Day -4 to 7, possible GVHD) and her other laboratory parameters do not strongly suggest that she was cirrhotic. Additionally, the diagnosis of venoocclusive disease is a consideration. Lastly, there were other potential reasons for the subject to develop edema and altered mental status (IV

fluids/medications and opiates, respectively), though the presence of ascites suggests some liver pathology.

Among the subjects who received ≥ 7 consecutive days of IV therapy, there were 3 deaths that occurred due to AEs that started while a subject was receiving IV therapy. Two of these deaths occurred in the letermovir arm and one in the placebo arm. These subjects are briefly described below.

- 0014-102131 (letermovir): This is a 50 year old male with AML who was randomized to receive oral letermovir but was switched to IV letermovir on Day 3 for unspecified reasons. On Day 13, he developed SAEs of aspiration pneumonia and respiratory failure. He required mechanical ventilation beginning on Day 16 and study medication was discontinued due to ongoing respiratory failure on Day 25. His hospital course was also complicated by pneumothorax and severe mucosal inflammation. He was ultimately transitioned to comfort care and died on Day 25. The investigator assessed all events as not related to study drug.

- 0030-101862 (letermovir): This is a 49 year old male with CML who underwent HSCT and subsequently developed gastrointestinal GVHD on Day 10 of treatment with letermovir. He switched back and forth between IV and oral administration of letermovir but was receiving IV therapy at the time that GVHD was first reported. Due to the GVHD SAE, the study drug was discontinued on Day 23. He experienced several episodes of GVHD that were refractory to therapy. On Day 246 he reportedly became comatose and he then died on Day 251. Minimal information is provided regarding the etiology of the subject's coma. All that is known is that on Day 245, 2 days prior to going into a coma, he developed pulmonary edema. GVHD was considered the cause of death and it was not considered study drug related.

- 0147-100023 (placebo): This is a 48 year-old female with myelodysplastic syndrome. On Day 86 of treatment, she was diagnosed with *Pneumocystis jirovecii* pneumonia. She died from respiratory failure on Day 93. Study drug was continued until the Day of death. The event was assessed to be unrelated to study drug.

Reviewer comment: Based on the available information, I agree with the investigators' assessments that the above described SAEs and deaths were unlikely to be related to study drug.

<u>Common AEs associated with IV letermovir administration</u>

The most common non-serious AEs that were reported in subjects who received 7 or more consecutive days of IV therapy (during the period of IV therapy) are presented in the table below. Events that occurred in ≥ 2% greater proportion of subjects in the letermovir arm

compared to the placebo arm are in bold font.

Table 41. P001: Treatment-Emergent AEs occurring in ≥ 10% of Letermovir Subjects Receiving ≥ 7 Days of IV Therapy

Preferred Term	Letermovir N=72 N (%)	Placebo N=27 N (%)
Graft versus host disease	10 (13.9%)	6 (22.2%)
Diarrhea	**10 (13.9%)**	**3 (11.1%)**
Febrile neutropenia	9 (12.5%)	4 (14.8%)
Pyrexia	8 (11.1%)	5 (18.5%)
Hypertension	8 (11.1%)	3 (11.1%)
Mucosal inflammation	6 (8.3%)	5 (18.5%)
Headache	6 (8.3%)	2 (7.4%)
Rash	6 (8.3%)	2 (7.4%)
Abdominal pain	6 (8.3%)	2 (7.4%)
Stomatitis	5 (6.9%)	3 (11.1%)
Nausea	5 (6.9%)	3 (11.1%)
Hypokalemia	**5 (6.9%)**	**1 (3.7%)**
Fluid overload	**5 (6.9%)**	**1 (3.7%)**
Hyperglycemia	**5 (6.9%)**	**1 (3.7%)**
Cough	**5 (6.9%)**	**0 (0.0%)**
Edema peripheral	**5 (6.9%)**	**0 (0.0%)**
Hematuria	4 (5.6%)	1 (3.7%)
Viremia*	4 (5.6%)	1 (3.7%)

Source: AEPLUS dataset
*Viremia does not refer to CMV viremia. In the letermovir arm, there were 3 subjects with HHV-6 viremia and one with herpes simplex viremia. In the placebo arm there was one subject with BK virus viremia.

There is significant overlap in the most common AEs reported among those subjects who received 7 or more consecutive days of IV therapy and among the safety population as a whole. The rate of AEs was generally lower in the IV therapy subpopulation, likely because these analyses only take into account AEs that occurred during the period of IV therapy, whereas analyses of the overall population include events from the entire treatment window. Events that were notably more common in the IV letermovir arm than the IV placebo arm were diarrhea, hypokalemia, fluid overload, hyperglycemia, cough, and edema peripheral. Notably, edema peripheral, diarrhea and cough were more common in the letermovir arm in the overall safety analysis as well. As laboratory abnormalities reported as AEs are generally unreliable, the ADLB dataset was used to assess for hyperglycemia and hypokalemia based on laboratory

results. Analysis of laboratory results confirmed an increase in hyperglycemia in the letermovir arm but did not identify an increase in hypokalemia in the letermovir arm.

Two subjects receiving IV letermovir experienced infusion site reactions. One subject experienced infusion site erythema and the other experienced inflammation. Both events were mild in severity. In addition to infusion site reactions, a single subject (0064-102010) experienced dyspnea (moderate) and hypersensitivity (mild) AEs. These events were non-serious and occurred on the first day the subject received IV letermovir (had received 4 days of oral letermovir and was then switched to IV letermovir). The study medication was discontinued following the hypersensitivity reaction and the events were considered resolved the following day.

IV letermovir and renal insufficiency

A safety concern specific to the IV formulation of letermovir is the potential for the hydroxypropyl β-cyclodextrin (HP β-CD) component of the solution to impact renal function. HP β-CD has been associated with nephrotoxicity in animals and has been shown to accumulate in humans with renal impairment. The IV placebo was normal saline and would not have contained HP β-CD. In P001, while Grade 4 changes in serum creatinine were more common in the IV placebo arm, any Grade changes in creatinine were more common in the IV letermovir arm (see table below). However, among subjects receiving only oral therapy, the rate of any Grade changes in creatinine was also found to be higher in the letermovir arm than the placebo arm, suggesting that the increased rate of and Grade creatinine abnormalities among subjects receiving letermovir is not attributable to the HP β-CD contained in the IV letermovir formulation.

Table 42. P001: Treatment-Emergent Abnormalities in Creatinine and Blood Urea Nitrogen (BUN) by Highest Toxicity Grade

Laboratory Parameter	Subjects Who Received Only Oral Therapy		Subjects Who Received Any IV* Therapy		Subjects Who Received ≥ 7 Consecutive Days IV* Therapy	
	Letermovir N = 274	Placebo N = 144	Letermovir N = 99	Placebo N = 48	Letermovir N = 72	Placebo N = 27
Creatinine (mg/dL)						
Grade 1 (1.1 to 1.3 x ULN)	3 (1.1%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Grade 2 (>1.3 to 1.8 x ULN or increase of >0.3 mg/dL above baseline)	36 (13.1%)	14 (9.7%)	7 (7.1%)	3 (6.3%)	7 (9.7%)	1 (3.7%)
Grade 3 (>1.8 to <3.5 x ULN or increase of 1.5 to <2.0 x baseline)	78 (28.5%)	41 (28.5%)	24 (24.2%)	14 (29.2%)	18 (25.0%)	6 (22.2%)
Grade 4 (≥3.5 x ULN or increase of ≥2.0 x baseline)	41 (15.0%)	15 (10.4%)	34 (34.3%)	16 (33.3%)	27 (37.5%)	11 (40.7%)
Any Grade	158 (57.7%)	70 (48.6%)	66 (66.7%)	33 (68.8%)	53 (73.6%)	18 (66.7%)
BUN (mg/dL)						
Grade 1 (23-26 mg/dL)	39 (14.2%)	17 (11.8%)	15 (15.2%)	5 (10.4%)	13 (18.1%)	2 (7.4%)
Grade 2 (27 – 31 mg/dL)	35 (12.8%)	23 (16.0%)	7 (7.1%)	2 (4.2%)	7 (9.7%)	1 (3.7%)
Grade 3 (> 31 mg/dL)	45 (16.4%)	24 (16.7%)	23 (23.2%)	15 (31.3%)	16 (22.2%)	8 (29.6%)
Any Grade	119 (43.4%)	64 (44.4%)	45 (45.5%)	22 (45.8%)	36 (50.0%)	11 (40.7%)

Source: ADLB dataset

* Includes all on-treatment laboratory values (not just those while receiving IV therapy).

The rate of renal AEs among subjects who received 7 or more days of IV therapy was also explored. Using the narrow Acute Renal Failure SMQ, it was determined that the rate of acute renal failure events was higher in subjects receiving IV placebo (29.6%) compared to subjects receiving IV letermovir (22.2%). However, it should be noted that this analysis includes all events occurring during the treatment period, not just those during the period of IV administration (this type of analysis was not possible with the available datasets in JReview using SMQs). A related analysis of AEs under the Renal and Urinary System Organ Class revealed that during the period of IV administration, AEs were more common in subjects receiving IV letermovir (15.3%) than subjects receiving IV placebo (11.1%). This System Organ Class-based analysis includes urinary events not indicative of renal failure (e.g. dysuria, urge incontinence) and does not include AEs under the Investigations System Organ Class that may be indicative of renal failure. Therefore, this analysis is less reliable than the SMQ-based analysis.

The Applicant performed several exposure –safety analyses on the data from an intensive PK subset of subjects in Trial P001. Among the intensive PK subset of subjects who had received 1 or more dose of IV letermovir, an association was detected between the letermovir Cmax and renal failure. However, the frequency of the renal failure AE within each Cmax quartile was highly variable, calling into question the accuracy of the model. No other exposure – safety analyses were performed on the subset of subjects receiving 1 or more doses of IV letermovir.

Additionally, among 5 subjects with renal impairment (estimated glomerular filtration rate of < 60 ml/min/1.73 m^2) who received at least one dose of IV letermovir, there was no worsening of the subject's renal function while receiving IV therapy. There were no subjects with renal impairment in the IV placebo arm, therefore a comparison of the rates of AEs between the renally impaired subjects receiving IV letermovir and those receiving IV placebo is not possible.

Reviewer Comment: The only potential safety signal present in the IV letermovir cohort that is not also present in the overall letermovir cohort is hyperglycemia (which was likely due to the use of 5% dextrose to dilute the IV letermovir solution in some subjects). However, the size of the IV safety database is small and the duration of IV exposure is short. Further, the amount of safety data regarding use of the IV formulation in patients with renal insufficiency is particularly limited and may be important given concerns surrounding HP β-CD. *This reviewer thinks that additional safety data for the IV formulation of letermovir are needed and a post-marketing requirement (PMR) should be considered. The limited availability of safety data for the IV formulation should be described in the package insert. Further, a statement recommending that exposure to the IV letermovir formulation be limited may be considered.*

8.5.2. **Cardiac Events**

Review of the most commonly reported individual PTs in Trial P001 does not suggest an

increase in cardiac events associated with letermovir use. However, when looking at the SOC level, a numerical imbalance of events falling under the cardiac disorders SOC is detected between the placebo and letermovir arms. During the treatment phase, cardiac disorders were reported in 12.6% of subjects receiving letermovir, compared to 6.3% of subjects receiving placebo. This imbalance persisted through week 24, at which point cardiac AEs were reported in 13.7% of the letermovir arm and 9.9% of the placebo arm. The Applicant noted this imbalance and conducted a post-hoc cardiac safety assessment. Following the completion of their assessment, the Applicant concluded that there is no evidence for a causal association between letermovir and cardiac disorders. A summary of our internal review of this potential safety signal is presented below.

Nonclinical

There were no major cardiac findings in the nonclinical studies of letermovir. A single animal in a 4-week intravenous study in monkeys experienced premature ventricular contractions of unclear significance. Please refer to the review of David McMillan, PhD, for additional information regarding the nonclinical development program.

Phase 1 Clinical Trials

Across Phase 1 trials, 668 subjects were exposed to letermovir. These subjects were predominately healthy volunteers, but some trials enrolled subjects with hepatic or renal impairment. There were no deaths and no cardiac SAEs reported in any Phase 1 trial.

Phase 2a Clinical Trial: Trial P019

As described previously, trial P019 enrolled 28 transplant (predominately kidney transplant) recipients and all subjects received letermovir or valganciclovir for (b) (4) for approximately 14 days. The doses used in this trial were markedly lower than those used in the Phase 3 trial (80 mg daily vs 480 mg daily). There were no cardiac AEs reported in P019.

Phase 2b Clinical Trial: Trial P020

In trial P020, 131 HSCT recipients received 12 weeks of letermovir or placebo for the prevention of CMV infection. The doses used in this trial were lower than those used in the Phase 3 trial (with the exception of a small number of P020 subjects who were receiving letermovir 240 mg daily with cyclosporine). All treatment-emergent cardiac AEs, regardless of severity and causality, are presented in the table below. Tachycardia was the most common cardiac AE, but the frequency of tachycardia events did not appear to increase with increasing letermovir dose. In fact, there were no tachycardia events in the highest letermovir dose arm. All other cardiac AEs were uncommon, occurring in no more than a single subject per arm.

Table 43. P020: Treatment-Emergent Cardiac AEs

Preferred Term	Letermovir 60 mg N = 33	Letermovir 120 mg N = 31	Letermovir 240 mg N = 34	Letermovir All N = 98	Placebo N = 33
Tachycardia	2 (6.1%)	3 (9.7%)	0 (0.0%)	5 (5.1%)	0 (0.0%)
Angina pectoris	0 (0.0%)	1 (3.2%)	1 (2.9%)	2 (2.0%)	0 (0.0%)
Pericardial effusion	1 (3.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Pericarditis	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (1.0%)	0 (0.0%)
Sinus arrhythmia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)

Source: ADAE dataset

None of the treatment-emergent cardiac events in Trial P020 were assessed by the investigator to be definitely, probably, or possibly related to study drug. Further, none of the cardiac AEs led to study drug discontinuation. The majority of the cardiac events occurring in Trial P020 were mild in severity. There was a moderate event of angina pectoris in the 240 mg letermovir arm and a severe event of angina pectoris in the 120 mg letermovir arm. There was also a moderate tachycardia event in the 60 mg letermovir arm and a severe pericarditis event in the 240 mg letermovir arm. The severe pericarditis event resulted in hospitalization and was therefore was considered an SAE. This was the only cardiac SAE in Trial P020. There were no deaths due to cardiac events in Trial P020.

Phase 3 Clinical Trial: Trial P001

As stated above, adverse events in the cardiac disorders system organ class were more common in the letermovir arm than in the placebo arm in Trial P001. All treatment-emergent cardiac events, regardless of severity or causality, are presented in the table below. The most commonly reported cardiac PTs were tachycardia and atrial fibrillation which had a numerically higher incidence in the letermovir arm compared to the placebo arm.

Table 44. P001: Treatment-Emergent Cardiac Events

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Tachycardia	15 (4.0%)	4 (2.1%)
Atrial fibrillation	13 (3.5%)	2 (1.0%)
Sinus tachycardia	4 (1.1%)	3 (1.6%)
Cardiac failure	5 (1.3%)	0 (0.0%)
Atrial flutter	4 (1.1%)	0 (0.0%)
Pericardial effusion	3 (0.8%)	1 (0.5%)
Bradycardia	2 (0.5%)	1 (0.5%)
Arrhythmia	3 (0.8%)	0 (0.0%)
Palpitations	2 (0.5%)	0 (0.0%)
Cardiovascular disorder	1 (0.3%)	0 (0.0%)
Myocarditis	1 (0.3%)	0 (0.0%)

Cardiomyopathy	1 (0.3%)	0 (0.0%)
Cardiac failure congestive	1 (0.3%)	0 (0.0%)
Pericarditis	1 (0.3%)	0 (0.0%)
Sinus node dysfunction	1 (0.3%)	0 (0.0%)
Cardiac failure acute	1 (0.3%)	0 (0.0%)
Atrioventricular block	1 (0.3%)	0 (0.0%)
Torsade de pointes	1 (0.3%)	0 (0.0%)
Ventricular tachycardia	1 (0.3%)	0 (0.0%)
Atrial hypertrophy	0 (0.0%)	1 (0.5%)
Cardiogenic shock	0 (0.0%)	1 (0.5%)
Left ventricular hypertrophy	0 (0.0%)	1 (0.5%)

Source: AEPLUS dataset

Individual PTs were grouped together into the broader categories of arrhythmia events and heart failure events for further analysis:

- Arrhythmia events: If all tachyarrhythmia PTs (tachycardia, atrial fibrillation, sinus tachycardia, atrial flutter, torsade de pointes, and ventricular tachycardia) are combined, 35 (9.4%) subjects in the letermovir arm experienced 38 tachyarrhythmia events compared to 9 (4.7%) subjects experiencing 9 tachyarrhythmia events in the placebo arm. Further, if all arrhythmia PTs (tachycardia, atrial fibrillation, sinus tachycardia, atrial flutter, ventricular tachycardia, bradycardia, arrhythmia, sinus node dysfunction, atrioventricular block, and torsade de pointes) are combined, 38 (10.2%) of letermovir subjects experienced 45 arrhythmia events compared to 10 (5.2%) of placebo subjects who experienced 10 arrhythmia events.

- Heart failure events: A total of 7 (1.9%) subjects in the letermovir arm and 1 (0.5%) subject in the placebo arm experienced one or more of the following heart failure events in the cardiac SOC: cardiac failure, cardiac failure acute, cardiac failure congestive, cardiogenic shock, and cardiomyopathy. Using the narrow heart failure SMQ, which pulls relevant PTs from outside of the Cardiac disorders SOC (e.g. pulmonary edema), the rate of treatment-emergent heart failure events was similar, 3.2% and 2.6% in the letermovir and placebo arms, respectively. None of the heart failure events were assessed to be drug-related and only one heart failure event (PT = cardiac failure, in letermovir arm) led to study drug discontinuation. Two of the heart failure events (cardiac failure in the letermovir arm and the cardiogenic shock in the placebo arm) were fatal. The letermovir subject experiencing a heart failure event that resulted in study drug discontinuation and ultimately death is described in detail below (Subject 0164-102037).

There was overlap between subjects experiencing heart failure events and subjects experiencing arrhythmias. In the letermovir arm, 4 of the 7 subjects with heart failure events also experienced an arrhythmia.

There was no apparent trend regarding the time to onset of cardiac events. The majority of the treatment-emergent cardiac AEs were mild and non-serious in nature. Severe cardiac AEs were reported in 7 (1.9%) and 1 (0.5%) subjects in the letermovir and placebo arms, respectively. Cardiac SAEs occurred in 6 (1.6%) subjects in the letermovir arm and 1 (0.5%) subject in the placebo arm. The following cardiac SAEs each occurred in one subject in the letermovir arm: atrial fibrillation, atrial flutter, cardiac failure, pericarditis, sinus node dysfunction, and arrhythmia. One placebo subject experienced a cardiogenic shock SAE. There were only 2 cardiac events that resulted in death, one in a placebo subject and one in a letermovir subject (the previously noted heart failure events). The Sponsor provided brief narratives for all cardiac SAEs that are summarized below.

Cardiac SAE brief narratives:

- Subject 0164-102037 (letermovir): This is a 60 year-old man with a history of diffuse large B-cell lymphoma, chronic heart failure, and diabetes who experienced an SAE of progression of heart failure on Day 2 of treatment. On the same day, he was diagnosed with sepsis. Then on Day 4, he developed abnormalities in his liver laboratory parameters (peak ALT = 1156 IU/L, AST = 2668 IU/L, bilirubin = 2.6 mg/dL). Study drug was discontinued on Day 5. He experienced progressive multi-organ failure and ultimately died on Day 12 due to cardiac failure. This subject had recently received fludarabine (Day -12) which has been associated with heart failure.

- Subject 0063-100092 (letermovir): This is a 71 year-old male with a history of atrial fibrillation who experienced sinus node dysfunction on Day 2. The cardiac event resolved in approximately 1 hour and no action was taken with study drug. The subject went on to experience a fatal sepsis event (bronchopulmonary aspergillosis) starting on Day 3.

- Subject 0058-100130 (letermovir): This is a 62 year-old male with a history of atrial fibrillation and diastolic dysfunction. On Day 81 he experienced an unspecified arrhythmia. The study drug was continued and the event resolved within 1 day.

- Subject 0045-101673 (letermovir): This is a 50 year-old female with myelodysplastic syndrome and no cardiac history who experienced two episodes of pericarditis on Day 21 and Day 102. Study medication was continued through the first event and study drug had already been completed by the time of the second event. There were no apparent underlying medical conditions that would have predisposed the subject to pericarditis. However, she had received methotrexate approximately 2 weeks prior to the first episode of pericarditis and methotrexate has been associated with pericarditis.

- Subject 0101-101682 (letermovir): This is a 55 year-old male with a history of endocarditis who developed atrial fibrillation on Day 70. No action was taken with the

study medication and the atrial fibrillation resolved in less than one day. The subject's history of endocarditis may have predisposed him to atrial fibrillation. He had also received fludarabine which has been associated with arrhythmia and supraventricular tachycardia and busulfan which has been associated with atrial fibrillation. However, these medications had been administered 2-3 months prior to the onset of atrial fibrillation.

- Subject 0122-102078 (letermovir): This is a 61 year-old male with a history of sinus bradycardia. He experienced atrial flutter on Day 77, one day after he completed letermovir therapy. The event resolved on Day 85. The subject was receiving nifedipine which is associated with palpitations and rarely arrhythmias. He also had remote exposure to fludarabine, which as previously mentioned has been associated with arrhythmias.

- Subject 0030-100334 (placebo): This is a 48 year-old male with no cardiac history who experienced pneumonia and cardiogenic shock on Day 14 (of note, study drug had been stopped on Day 13 due to diarrhea). He died on Day 15 and death was attributed to cardiogenic shock. He had received fludarabine on Days -6 to -4, which is associated with heart failure.

Reviewer comment: The majority of the cases of cardiac AEs described above are confounded by pre-existing medical conditions and the use of other medications with known cardiac side effects. I agree with the investigators' assessment that these events were not 'definitely' or 'probably' study drug-related.

Among the treatment-emergent AEs under the cardiac disorders SOC, only 1 event was considered drug related: 1 bradycardia event in the placebo arm. Similarly, only one cardiac event led to study drug discontinuation (Subject 0164-102037).

During the primary follow-up period (Week 16 – 24), there were an additional 5 (1.3%) letermovir subjects and 7 (3.7%) placebo subjects who experienced cardiac events. Only one of these was serious (cardiac arrest in a placebo subject) and none were assessed to be drug related. Of note, there was one letermovir subject who experienced a myocardial infarction (MI) in this primary follow-up period. This subject had no cardiac history though his conditioning regimen had contained cardiotoxic agents. He experienced an MI on Day 75 and his last exposure to letermovir had been on Day 5 (discontinued due to cerebral hemorrhage). The MI was not serious and was mild in severity.

<u>Cardiac Events and Intravenous Administration</u>

It was noted in Trial P001 that letermovir exposure was approximately 3-fold higher with IV administration compared to oral administration. We therefore looked closely at cardiac events

occurring in subjects who received IV letermovir to see if perhaps the increase in exposure associated with IV administration could be playing a role in the disproportionate number of cardiac events observed in the letermovir arm. There were 99 subjects who received 7 or more consecutive days of IV study drug (72 in the letermovir arm, 27 in the placebo arm). During the period of IV administration, 11 (15.3%) subjects in the letermovir arm experienced AEs under the cardiac disorders body system class, whereas 0 (0.0%) subjects in the placebo arm experienced cardiac events. When the subjects who received 7 consecutive days of IV therapy are excluded, the imbalance in the proportion of subjects experiencing treatment-emergent cardiac events between the letermovir and placebo arms (27/301, 9.0% and 11/165, 6.7%, respectively) is less pronounced. The cardiac events experienced by the subjects receiving 7 or more days of IV letermovir are presented in the table below. Of note, only those events occurring during the period of IV administration are included in the table. The types and rates of cardiac events observed in subjects receiving IV therapy are similar to those observed in the overall letermovir population.

Table 45. Cardiac Events in Subjects Receiving ≥ 7 Consecutive Days of IV Letermovir

Preferred Term	Letermovir N=72 N (%)	Placebo N=27 N (%)
Tachycardia	3 (4.2%)	0 (0.0%)
Atrial fibrillation	2 (2.8%)	0 (0.0%)
Palpitations	2 (2.8%)	0 (0.0%)
Cardiac failure congestive	1 (1.4%)	0 (0.0%)
Myocarditis	1 (1.4%)	0 (0.0%)
Pericardial effusion	1 (1.4%)	0 (0.0%)
Sinus tachycardia	1 (1.4%)	0 (0.0%)
Torsade de pointes	1 (1.4%)	0 (0.0%)
Ventricular tachycardia	1 (1.4%)	0 (0.0%)

Source: AEPLUS dataset

Reviewer comment: The increased rate of cardiac events observed in subjects receiving IV letermovir may be partially attributable to the fact that subjects who need IV therapy are often more acutely ill and therefore at increased risk for cardiac events as compared to subjects who are able to take oral therapy. However, under this premise, you would expect an increase in the rate of cardiac events among subjects receiving IV placebo as well, which was not observed. Alternatively, the increased rate of cardiac events observed in subjects receiving IV letermovir may be in part due to the increased letermovir exposure associated with IV administration. This is supported by the Applicant's exposure – safety analysis which revealed an association between the letermovir C_{max} and cardiac disorders and arrhythmias. See Section 8.11 for additional exposure –safety analyses findings.

None of the cardiac events occurring during IV therapy were assessed to be study drug related and none led to treatment discontinuation. Only one of these cardiac events was considered serious (atrial fibrillation).

Differences in demographics and cardiac history

Baseline characteristics that may impact cardiovascular risk (e.g., age, race, and body mass index) were similar in the letermovir and placebo arms. Differences in cardiac history as reported at baseline were also compared across arms (see table below). In the safety population, cardiac medical history conditions were more common in the letermovir arm than in the placebo arm (112 (30.0%) and 49 (25.5%) subjects reported one or more cardiac medical history conditions in the letermovir and placebo arms, respectively). The most commonly reported cardiac medical history terms are displayed in the table below. The three most common cardiac medical history terms are all tachyarrhythmias (tachycardia, atrial fibrillation, and sinus tachycardia). Numerically, tachycardia and atrial fibrillation appear somewhat more common in the letermovir arm. However, overall, there are no discernable major differences between the two arms regarding cardiac medical history.

Table 46. P001: The Most Common Cardiac Medical History among ASaT Population

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Tachycardia	27 (7.2%)	13 (6.8%)
Atrial fibrillation	20 (5.4%)	5 (2.6%)
Sinus tachycardia	9 (2.4%)	7 (3.7%)
Palpitations	10 (2.7%)	4 (2.1%)
Mitral valve incompetence	9 (2.4%)	4 (2.1%)
Bradycardia	9 (2.4%)	1 (0.5%)
Tricuspid valve incompetence	7 (1.9%)	3 (1.6%)

Source: MH dataset

The Applicant's post-hoc cardiac analysis included an assessment of the effect of baseline cardiac conditions on the incidence of cardiac AEs in trial P001. They determined that among subjects with a cardiac history, the rate of treatment-emergent cardiac events was markedly higher in the letermovir group than in the placebo group (21.4% vs 6.1%, respectively). Among subjects without a cardiac history, the rate of treatment-emergent cardiac events was similar in the letermovir and placebo arms (8.8% vs 6.3%, respectively). Based on these analyses, it appears that the rate of cardiac events in the placebo arm was similar regardless of cardiac history, but the rate of cardiac events in the letermovir arm was impacted by cardiac history. Further analyses revealed that among the subset of subjects who experienced a cardiac AE, the proportion of subjects with cardiac medical history was higher in the letermovir arm than in the

placebo arm (24/47, 51.1% and 3/12, 25.0%, respectively). The most common cardiac medical history terms reported by subjects who experienced a cardiac AE are presented by arm in the table below.

Table 47. P001: Cardiac Medical History Terms Reported in ≥ 2 Subjects Experiencing Cardiac Adverse Events

Preferred Term	Letermovir N=47 N (%)	Placebo N=12 N (%)
Atrial fibrillation	6 (12.8%)	1 (8.3%)
Palpitations	3 (6.4%)	1 (8.3%)
Bradycardia	3 (6.4%)	0 (0.0%)
Sinus tachycardia	2 (4.3%)	1 (8.3%)
Tachycardia	3 (6.4%)	0 (0.0%)
Coronary artery disease	2 (4.3%)	0 (0.0%)
Diastolic dysfunction	2 (4.3%)	0 (0.0%)
Sinus bradycardia	2 (4.3%)	0 (0.0%)

Source: AEPLUS and MH datasets

48 Week CSR Data

No additional cardiac SAEs occurred between Week 24 and Week 48.

Division of Cardiovascular and Renal Products (DCRP) Consultation

DCRP was consulted to assist DAVP with interpretation of the available data regarding cardiac events and to give recommendations regarding appropriate labeling and potential future studies. In summary, the DCRP reviewer concluded that the observed imbalance of cardiac events may be drug-induced. Therefore, the reviewer recommended including a general description of the reported cardiac events in the letermovir package insert. No additional studies were recommended by the reviewer.

In addition to the above recommendations, the DCRP reviewer observed that while the difference in all-cause mortality rates between the two arms narrowed from Week 24 to Week 48, the difference in CMV-related mortality was stable from Week 24 to Week 48. Based on this observation, the DCRP reviewer concluded that there may be a higher rate of non-CMV-related mortality in the letermovir arm compared to the placebo arm between Week 24 and 48.

In response to the DCRP consult, this reviewer closely examined the deaths in all study periods, including the Week 24 - 48 window. Individual PTs that resulted in death were grouped together in categories such as relapse-related, GVHD, and infection, as shown in the table below.

Table 48. P001: Category of AE Resulting in Death (ASaT Population, Through Database Lock)

Category of AE Resulting in Death	Study Window in which Death Occurred							
	Weeks 0 – 16 (On-treatment)		Weeks 16 - 24		Weeks 24 - 48		Weeks 16 – 48	
	Letermovir N=373	Placebo N=192	Letermovir N=373	Placebo N=192	Letermovir N=373	Placebo N=192	Letermovir N=373	Placebo N=192
Total number of deaths[+]	17 (4.6%)	12 (6.3%)	31 (8.3%)	23 (12.0%)	22 (5.9%)	9 (4.7%)	53 (14.2%)	32 (16.7%)
Relapse-related	3 (0.8%)	2 (1.0%)	16 (4.3%)	11 (5.7%)	8 (2.1%)	3 (1.6%)	24 (6.4%)	14 (7.3%)
GVHD	1 (0.3%)	2 (1.0%)	2 (0.5%)	3 (1.6%)	5 (1.3%)	2 (1.0%)	7 (1.9%)	5 (2.6%)
Infection	7 (1.9%)	6 (3.1%)	11 (2.9%)	4 (2.1%)	8 (2.1%)	3 (1.6%)	19 (5.1%)	7 (3.6%)
VOD	2 (0.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac-related*	1 (0.3%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Pulmonary-related	2 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.3%)	1 (0.5%)	1 (0.3%)	2 (1.0%)
Kidney-related	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Liver-related (non-VOD)	1 (0.3%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bleeding event or hematologic abnormality	1 (0.3%)	0 (0.0%)	1 (0.3%)	2 (1.0%)	0 (0.0%)	1 (0.5%)	1 (0.3%)	3 (1.6%)
MODS	0 (0.0%)	1 (0.5%)	1 (0.3%)	2 (1.0%)	1 (0.3%)	0 (0.0%)	2 (0.5%)	2 (1.0%)
Other**	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	3 (0.8%)	0 (0.0%)

Source: P001v01 ADLS and AEPLUS datasets
[+]Subjects may have more than one fatal AE
*Cardiac deaths: On treatment: cardiac failure, n = 1 (letermovir), cardiogenic shock, n = 1 (placebo); Weeks 16 – 14: cardiac arrest, n = 1 (placebo)
**Other: failure to thrive (n = 1, letermovir), hypokalemia (n = 1, letermovir), and pancreatitis (n = 1, letermovir)
Abbreviations: MODS, multiple organ dysfunction syndrome; VOD, venoocclusive disease

This table shows that malignancy relapse, infection, and GVHD were the most common events leading to death across all study windows. Cardiac events were uncommon in both arms and all occurred prior to Week 24. Please note that the table includes only deaths that occurred on-study. Deaths that occurred after subjects were withdrawn from the study or had completed the study are not included (even if the AE that resulted in death started on-study). However, review of the post-study deaths identified only a single death that was cardiovascular in nature (subject 0091-102193 in the letermovir arm experienced a cerebrovascular accident on Day 373 and died the same day).

Reviewer Comment: The above table suggests that there is no major shift in the causes of death during the Week 24 to 48 window. The slightly higher proportion of letermovir subjects compared to placebo subjects dying from Week 24 to 48 (5.9% and 4.7% in the letermovir arm and placebo arm, respectively) is not attributable to cardiac events based on the available data. Further, this reviewer is leery of analyses of CMV-related and non-CMV-related mortality as these are artificial designations that have uncertain clinical meaningfulness (recall that CMV-related mortality is defined as death in any subject who met the primary endpoint).

In conclusion, the clinical significance of the observed increased frequency of cardiac events in the letermovir arm of Trial P001 is unclear. The majority of these events were non-serious and of mild to moderate severity. HSCT recipients are incredibly complex and frequently have a high acuity of illness. The majority of the cardiac events were confounded by concomitant use of known cardiotoxic medications (e.g. fludarabine, busulfan, and methotrexate), cardiac history, and acute infections which may predispose to arrhythmias and ventricular dysfunction. Additionally, it appears that there may have been some imbalance in the proportion of subjects with baseline cardiac conditions between the letermovir and placebo arm. Nonetheless, it is possible that the increased proportion of subjects experiencing cardiac events in the letermovir arm is due to a drug-effect. Therefore, this reviewer agrees with the DCRP reviewer that the cardiac AEs should be included in the letermovir package insert. Specifically, it is anticipated that the overall rate of cardiac AEs as well as the rate of the most common cardiac PTs reported more often in letermovir subjects (tachycardia and atrial fibrillation) will be presented. Notably, although the rate of the PT Cardiac failure appears to be more common in subjects receiving letermovir, when heart failure PTs are combined using the narrow heart failure SMQ, the rate of events is comparable between arms. Therefore, it is not anticipated that heart failure will be included in the package insert.

Given the predominately non-serious nature of the observed cardiac events as well as the significant confounding associated with a majority of the cardiac events, this reviewer does not believe the cardiac events should be described under the Warnings and Precautions section of the package insert. A general description of cardiac events in the Adverse Reactions section seems sufficient at this time.

Reviewer Comment: The potential cardiac toxicity of letermovir does not offset the clear clinical benefit of the CMV infection prevention provided by letermovir. Therefore, this potential cardiac toxicity should not impact the approvability of letermovir.

8.5.3. Ear and Labyrinth Events

The Applicant also noted that there was an imbalance in the rate of AEs under the Ear and Labyrinth SOC (4.6% of subjects in the letermovir arm and 1.0% of subjects in the placebo arm). This imbalance was confirmed by our internal analysis. All reported Ear and Labyrinth AEs are presented in the table below. At the PT level, the individual terms that appeared numerically more common in the letermovir arm were vertigo and ear pain/discomfort. The PT dizziness was investigated as a potential alternative means of reporting vertigo events and it was determined that the rate of dizziness was similar in the two arms (6.7% in the letermovir arm and 5.7% in the placebo arm). Two of the 5 cases of vertigo were assessed by the investigator as being related to study drug. None of the vertigo events or other ear and labyrinth events were serious or led to treatment discontinuation. Of note, two of the vertigo cases were confounded by concomitant cyclosporine use, which has been associated with vestibular disturbances in rheumatoid arthritis and solid organ transplant populations. Regarding the ear pain and ear discomfort AEs, the etiology is unclear. Analysis of infections involving the ear (PTs ear infection, otitis externa, otitis media, and otitis media acute) revealed a similarly low rate of events (1.1% and 0.5% in the letermovir and placebo arms, respectively). Also of note, one of the subjects experiencing tinnitus was receiving amikacin around the time of the event, which is known to cause ototoxicity and vestibular toxicity.

Table 49. P001: Treatment-Emergent Ear and Labyrinth Events

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Vertigo	5 (1.3%)	0 (0.0%)
Ear pain	4 (1.1%)	1 (0.5%)
Ear discomfort	3 (0.8%)	0 (0.0%)
Hypoacusis	1 (0.3%)	1 (0.5%)
Tinnitus	2 (0.5%)	0 (0.0%)
Cerumen impaction	2 (0.5%)	0 (0.0%)
Deafness	1 (0.3%)	0 (0.0%)

Source: AEPLUS

In Trial P020, there were 4 (4.1%) letermovir subjects and 1 (3.0%) placebo subjects who experienced EAs under the Ear and labyrinth system organ class. Two of the four letermovir

subjects experiencing an event were in the lowest dose cohort, thus showing no dose-dependency. No ear and labyrinth PT was reported more than once.

Reviewer Comment: There may be a small numerical increase in the rate of vertigo and ear pain/discomfort in the letermovir arm as compared to the placebo arm in Trial P001. However, the small number of events precludes a conclusive assessment. Routine pharmacovigilance in the postmarketing realm can track this issue further, though given the generally non-serious nature of this event there may be underreporting.

8.5.4. Infection Events

Infections are a major source of morbidity and mortality in HSCT recipients due to the profound degree of immunosuppression occurring post-transplantation. Therefore, it is not surprising that infection-related AEs were common overall (in Trial P001, the Infections and Infestations SOC was the second most commonly implicated SOC, following the Gastrointestinal Disorders SOC). More importantly, many of the most common SAEs and AEs resulting in death were under the Infection and Infestations SOC. Upon first glance, it appears that events occurring under this SOC were more common in the placebo arm. However, further investigation reveals that the increase in infection AEs in the placebo arm was attributable to CMV infections. In Trial P001, after the exclusion of CMV infection, the proportion of subjects experiencing one or more infection AEs was actually higher in the letermovir arm (59.5% and 48.4% in the letermovir arm and placebo arm, respectively).

This imbalance in infection AEs prompted additional analyses of infection AEs. These additional analyses focused on SAEs. During the treatment period, excluding the PT CMV infection, there were 69 (18.5%) subjects in the letermovir arm and 25 (13.0%) subjects in the placebo arm who experienced treatment-emergent infection SAEs in Trial P001. The most common of these events are shown in the table below.

Table 50. P001: Treatment-Emergent Infection SAEs Occurring in > 0.5% of Letermovir Subjects

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Pneumonia	8 (2.1%)	3 (1.6%)
Septic shock	4 (1.1%)	5 (2.6%)
Sepsis	5 (1.3%)	2 (1.0%)
Staphylococcal bacteremia	3 (0.8%)	2 (1.0%)
Bronchopulmonary aspergillosis	3 (0.8%)	1 (0.5%)
Clostridium difficile colitis	3 (0.8%)	1 (0.5%)
Urinary tract infection	4 (1.1%)	0 (0.0%)
Epstein-Barr virus infection	3 (0.8%)	0 (0.0%)
Sinusitis	3 (0.8%)	0 (0.0%)

Source: AEPLUS dataset

Given the overall low rate of individual infection PTs, there are no discernable trends regarding specific PTs that may account for the overall increase in infection SAEs observed in the letermovir arm. However, certain related PTs may be combined as follows:

- Sepsis: Including PTs septic shock, sepsis, bacterial sepsis, Escherichia sepsis, and klebsiella sepsis, there were 10 (2.7%) letermovir subjects and 8 (4.2%) placebo subjects experiencing serious septic events.
- Bacteremia: Including PTs staphylococcal bacteremia, bacteremia, escherichia bacteremia, enterococcal bacteremia, bacterial sepsis, Escherichia sepsis, and klebsiella sepsis, 6 (1.6%) letermovir subjects and 6 (3.1%) placebo subjects experienced serious probable bacteremia events.
- Respiratory tract infections: Including PTs pneumonia, bronchopulmonary aspergillosis, sinusitis, respiratory tract infection viral, acute sinusitis, rhinovirus infection, pneumonia bacterial, pneumocystis jirovecii pneumonia, pharyngitis, pneumonia parainfluenza viral, pseudomonas bronchitis, respiratory tract infection, nasopharyngitis, bronchitis, and bronchiolitis, there were 25 (6.7%) letermovir subjects and 7 (3.6%) placebo subjects experiencing serious respiratory tract infections. Including only PTs suggestive of a bacterial lower respiratory tract infection (pneumonia, pneumonia bacterial, and pseudomonas bronchitis), there were 11 (2.9%) letermovir subjects and 3 (1.6%) placebo subjects identified.
- Fungal infections: Including PTs bronchopulmonary aspergillosis, pneumocystis jirovecii pneumonia, mucormycosis, aspergillus infection, and esophageal candidiasis, 6 (1.6%) letermovir subjects and 2 (1.0%) placebo subjects experienced serious fungal infections.
- Viral infections (non-CMV): Including PTs Epstein-Barr virus (EBV) infection, EBV viremia, respiratory tract infection viral, cystitis viral, meningoencephalitis herpetic, gastroenteritis viral, viral hemorrhagic cystitis, herpes zoster, rhinovirus infection, meningoencephalitis viral, adenoviral hemorrhagic cystitis, pneumonia parainfluenza viral, gastroenteritis rotavirus, viral infection, gastroenteritis norovirus, BK virus infection, and viremia there were 22 (5.9%) letermovir subjects and 6 (3.1%) placebo subjects experienced serious viral infections.

Reviewer Comment: Sepsis and bacteremia SAEs occurred more commonly in the placebo arm while respiratory tract infection and viral infection SAEs occurred more frequently in the letermovir arm. Fungal SAEs were relatively balanced between the two arms, with a slight numerical increase in the letermovir arm. Given the wide array of reported events, even after attempting to group infection SAEs together in more meaningful way, it is still difficult to interpret these data and to draw any certain conclusions. A broad statement regarding the increased risk of infection may be included in the letermovir label.

The risk of infection may be increased and prolonged in subjects requiring ongoing treatment for GVHD. Therefore, infections occurring in the primary and secondary follow-up period are also of interest. As described previously, only drug-related SAEs and fatal SAEs were collected after Week 16. There were no drug-related infection SAEs after week 16 but there were deaths due to infection events. Between Week 16 and the Week 48 database lock, there were 19 (5.1%) letermovir subjects and 7 (3.6%) placebo subjects who experienced infection AEs that led to death. Those AEs are shown in the table below.

Table 51. P001: Infection AEs Resulting in Death: Week 24- 48*

Preferred Term	Letermovir N=373 N (%)	Placebo N=192 N (%)
Pneumonia	5 (1.3%)	2 (1.0%)
Sepsis	3 (0.8%)	1 (0.5%)
Aspergillus infection	0 (0.0%)	1 (0.5%)
Atypical pneumonia	1 (0.3%)	0 (0.0%)
Bacteremia	1 (0.3%)	0 (0.0%)
Bronchopulmonary aspergillosis	1 (0.3%)	0 (0.0%)
Clostridium bacteremia	1 (0.3%)	0 (0.0%)
Fusarium infection	1 (0.3%)	0 (0.0%)
Mucormycosis	1 (0.3%)	0 (0.0%)
Neutropenic sepsis	1 (0.3%)	0 (0.0%)
Parainfluenza virus infection	1 (0.3%)	0 (0.0%)
Pneumonia bacterial	0 (0.0%)	1 (0.5%)
Pneumonia respiratory syncytial viral	1 (0.3%)	0 (0.0%)
Pneumonia staphylococcal	0 (0.0%)	1 (0.5%)
Pulmonary tuberculosis	0 (0.0%)	1 (0.5%)
Septic shock	1 (0.3%)	0 (0.0%)
Systemic candida	1 (0.3%)	0 (0.0%)

Source: P001v01 AEPLUS dataset
*AE began between Week 24 and Week 48, but in some cases death occurred after Week 48.

Reviewer Comment: The difference in the proportion of subjects experiencing infections that lead to death is small but notable. Unfortunately, due to the small number of events it is difficult to identify a specific type or location of infection that is driving this difference. Mechanistically, it is not clear how letermovir would be causing an increased rate of infection. As these deaths were due to AEs that started after Week 24 (therefore a minimum of 10 weeks after drug exposure), it seems unlikely that the infections are resulting from a direct drug toxicity. This reviewer is not able to speculate on a mechanism by which the reduction in CMV infections associated with letermovir would lead to an increase in other infections. In fact, the opposite finding would be expected based on the existing literature regarding the indirect

effects of CMV infection. As the overall mortality is significantly lower in the letermovir arm at Week 24 and numerically lower at Week 48, this slight increase in deaths due to an infection occurring weeks to months after the receipt of letermovir is of unclear clinical significance.

In Trial P020, the rate of treatment-emergent infections (excluding CMV-related infections) is as follows: 39.4% (letermovir 60 mg), 45.2% (letermovir 120 mg), 55.9% (letermovir 240 mg) and 48.5% (placebo). The rate of infection SAEs followed a similar pattern: 9.1% (letermovir 60 mg), 12.9% (letermovir 120 mg), 20.1% (letermovir 240 mg) and 18.2% (placebo).

Reviewer Comment: In Trial P020, the rate of overall infection adverse events and serious infection adverse events increases as the letermovir dose increases. However, the rate in the placebo arm is higher than the two lower letermovir dose arms. Therefore, no clear conclusions regarding a possible association between the letermovir dose and the rate of infections can be drawn from this data.

8.5.5. Testicular Toxicity

Preclinical fertility and embryonic development toxicology studies showed nonreversible testicular degeneration and reduced fertility indices in rats receiving high doses of letermovir. No testicular toxicity was observed in the 13-week fertility study in monkeys, or in any of the repeat dose general toxicology studies in monkeys or mice (though the study in mice was a general toxicity study, not a dedicated fertility/early embryonic study).

In the clinical trials, AEs potentially related to testicular toxicity were reported uncommonly. In Trial P020, there was a single subject in the letermovir 120 mg arm who experienced an on-treatment AE of blood testosterone decreased. In Trial P001, the following AEs were reported in the letermovir and placebo arms, respectively:

- Blood testosterone decreased: 5 (1.3%) vs 0 (0.0%)
- Erectile dysfunction: 2 (0.5%) vs 1 (0.5%)
- Libido decreased: 0 vs 1 (0.5%)

To further evaluate the testicular toxicity observed in preclinical studies, serum inhibin B, LH, FSH, and testosterone levels were measured at baseline, the end of treatment (i.e. 14 weeks post-transplant), and Week 24 post-transplant in Trial P001. The Applicant produced the following table to allow for a comparison of on-study shifts in each of these parameters between the letermovir and placebo group.

Table 52. P001: Shift in Sex Hormone Values from Baseline over Time

Parameter	Post-baseline Visit	Letermovir (N=163) Baseline				Placebo (N=92) Baseline			
		Low	Normal	High	Total	Low	Normal	High	Total
Follitropin (mIU/mL)									
End of Treatment	Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	2 (3.1%)	2 (3.1%)	4 (6.3%)	0 (0.0%)	1 (2.9%)	2 (5.7%)	3 (8.6%)
	High	0 (0.0%)	19 (29.7%)	41 (64.1%)	60 (93.8%)	0 (0.0%)	9 (25.7%)	23 (65.7%)	32 (91.4%)
	Total	0 (0.0%)	21 (32.8%)	43 (67.2%)	64 (100.0%)	0 (0.0%)	10 (28.6%)	25 (71.4%)	35 (100.0%)
Week 24	Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	2 (2.4%)
	High	0 (0.0%)	37 (26.8%)	99 (71.7%)	136 (98.6%)	1 (1.2%)	26 (31.0%)	55 (65.5%)	82 (97.6%)
	Total	0 (0.0%)	38 (27.5%)	100 (72.5%)	138 (100.0%)	1 (1.2%)	27 (32.1%)	56 (66.7%)	84 (100.0%)
Inhibin B (pg/mL)									
End of Treatment	Low	29 (49.2%)	23 (39.0%)	0 (0.0%)	52 (88.1%)	19 (57.6%)	7 (21.2%)	0 (0.0%)	26 (78.8%)
	Normal	0 (0.0%)	5 (8.5%)	2 (3.4%)	7 (11.9%)	0 (0.0%)	7 (21.2%)	0 (0.0%)	7 (21.2%)
	High	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	29 (49.2%)	28 (47.5%)	2 (3.4%)	59 (100.0%)	19 (57.6%)	14 (42.4%)	0 (0.0%)	33 (100.0%)
Week 24	Low	77 (58.3%)	41 (31.1%)	1 (0.8%)	119 (90.2%)	46 (60.5%)	22 (28.9%)	0 (0.0%)	68 (89.5%)
	Normal	1 (0.8%)	9 (6.8%)	2 (1.5%)	12 (9.1%)	0 (0.0%)	7 (9.2%)	0 (0.0%)	7 (9.2%)
	High	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Total	78 (59.1%)	50 (37.9%)	4 (3.0%)	132 (100.0%)	47 (61.8%)	29 (38.2%)	0 (0.0%)	76 (100.0%)

Parameter	Post-baseline Visit	Letermovir (N=163) Baseline				Placebo (N=92) Baseline			
		Low	Normal	High	Total	Low	Normal	High	Total
Luteinizing Hormone (mIU/mL)									
End of Treatment	Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	0 (0.0%)	36 (56.3%)	4 (6.3%)	40 (62.5%)	0 (0.0%)	15 (41.7%)	4 (11.1%)	19 (52.8%)
	High	0 (0.0%)	14 (21.9%)	10 (15.6%)	24 (37.5%)	0 (0.0%)	9 (25.0%)	8 (22.2%)	17 (47.2%)
	Total	0 (0.0%)	50 (78.1%)	14 (21.9%)	64 (100.0%)	0 (0.0%)	24 (66.7%)	12 (33.3%)	36 (100.0%)
Week 24	Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Normal	2 (1.4%)	63 (45.7%)	4 (2.9%)	69 (50.0%)	1 (1.2%)	33 (39.3%)	10 (11.9%)	44 (52.4%)
	High	0 (0.0%)	45 (32.6%)	24 (17.4%)	69 (50.0%)	0 (0.0%)	20 (23.8%)	20 (23.8%)	40 (47.6%)
	Total	2 (1.4%)	108 (78.3%)	28 (20.3%)	138 (100.0%)	1 (1.2%)	53 (63.1%)	30 (35.7%)	84 (100.0%)
Testosterone Total (ng/dL)									
End of Treatment	Low	8 (12.7%)	7 (11.1%)	0 (0.0%)	15 (23.8%)	1 (2.8%)	3 (8.3%)	1 (2.8%)	5 (13.9%)
	Normal	15 (23.8%)	24 (38.1%)	3 (4.8%)	42 (66.7%)	7 (19.4%)	22 (61.1%)	1 (2.8%)	30 (83.3%)
	High	2 (3.2%)	3 (4.8%)	1 (1.6%)	6 (9.5%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
	Total	25 (39.7%)	34 (54.0%)	4 (6.3%)	63 (100.0%)	8 (22.2%)	26 (72.2%)	2 (5.6%)	36 (100.0%)
Week 24	Low	13 (9.6%)	16 (11.8%)	1 (0.7%)	30 (22.1%)	12 (14.3%)	13 (15.5%)	0 (0.0%)	25 (29.8%)
	Normal	36 (26.5%)	57 (41.9%)	6 (4.4%)	99 (72.8%)	13 (15.5%)	35 (41.7%)	8 (9.5%)	56 (66.7%)
	High	1 (0.7%)	3 (2.2%)	3 (2.2%)	7 (5.1%)	0 (0.0%)	3 (3.6%)	0 (0.0%)	3 (3.6%)
	Total	50 (36.8%)	76 (55.9%)	10 (7.4%)	136 (100.0%)	25 (29.8%)	51 (60.7%)	8 (9.5%)	84 (100.0%)

Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with cyclosporin A.
N = Number of treated subjects with both a pre- and post-treatment sex hormones measurement.

Source: Applicant's P001v01 CSR

To help interpret the serum hormone results from Trial P001 and to aid in the determination of the need for a future study in which semen parameters would be evaluated, the Division of Bone, Reproductive and Urology Products (DBRUP) was consulted. Key comments from the DBRUP review are summarized below.

- Based on a lack of testicular toxicity in species other than the rat, as well as the absence of toxicity in rats receiving lower doses of letermovir, it appears likely that testicular toxicity is specific to the rat species and is associated with high doses only.
- There are no apparent clinically meaningful differences in sex hormone values between the two arms. However, these hormone concentrations do not reflect the health of the

seminiferous tubules or germinal epithelium and are not considered to be adequate biomarkers for germinal epithelial injury.

- It is anticipated that within the indicated population for letermovir, some patients will have previously received drugs with known testicular toxicity (primarily chemotherapeutic agents). These subjects may have semen analysis parameters that low at baseline. Additionally, some subjects may receive agents with testicular toxicity during the period of letermovir administration. Therefore, "it would be challenging, though not impossible, to conduct a human male testicular safety study."

Based on the above assessments, DBRUP made the following recommendations:

1. Describe the preclinical testicular toxicity findings in product labeling.
2. Consider including the difference in the rate of the clinical AE "testosterone decreased" in product labeling.

Reviewer Comment: Though there was a numerically greater proportion of subjects in the letermovir arm who went from normal serum inhibin b level at baseline to a low serum inhibin b level at the end of treatment than in the placebo arm, this difference was not clinically meaningful according to the DBRUP reviewer. Taking into consideration my review of the clinical data, interpretation of the preclinical data by our pharmacology-toxicology reviewer, and the conclusions of our DBRUP consultants, this reviewer does not believe that a PMR to conduct a study involving semen analysis is indicated. I agree with including the available non-clinical data in product labeling.

8.5.6. **Hepatobiliary Events**

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a mortality rate of 10-50%. Hepatocellular injury sufficient to impair bilirubin excretion has been used by the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as an indicator of clinical concern for drug-induced liver injury (DILI) includes: simultaneous ALT or AST > 3x ULN and total bilirubin > 2x ULN without an initial increase in alkaline phosphatase (< 2x ULN), and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury).

Trial P001:
The fulfillment of Hy's Law criteria was prespecified as an Event of Clinical Interest. There were 11 subjects that met Hy's Law criteria based on the laboratory criteria of the definition provided above. Eight (2.1%) subjects were in the letermovir arm and 3 (1.6%) subjects were in the placebo arm. These 11 cases are summarized in the table below.

Table 53. P001: Subjects Fulfilling Hy's Law Criteria

Subject/ Arm	Study Day Hy's Law Criteria Met	Dechallenge and Rechallenge Results	Alternative Etiology of LFT Abnormalities
100419 Letermovir	21	Study drug was stopped on Day 31. Subject had progressive liver dysfunction leading to death on Day 37.	Venoocclusive disease, sepsis
100401 Letermovir	22	Study drug held starting on Day 20. Patient developed fulminant hepatic failure and died on Day 24.	Venoocclusive disease, possible hepatic GVHD
100092 Letermovir	8	Study drug was stopped on Day 6 due to sepsis. Subject died on Day 13 from sepsis.	Sepsis, broncho-pulmonary aspergillosis
101957 Letermovir	5	Study drug was held starting Day 5, then resumed on Day 10. By Day 25 acute liver injury was resolved.	Engraftment syndrome
100335 Letermovir	19	Study drug was continued through LFT elevation. LFTs remained elevated on Day 83 and Day 344.	Amphotericin B and caspofungin use
102042 Letermovir	24	Study drug was continued throughout LFT elevation. Abnormal hepatic dysfunction AE resolved by Day 55.	Sepsis
100355 Letermovir	39	Study drug was continued throughout LFT elevation. On Day 94 the AE abnormal hepatic function was resolved (LFTs improved while still on letermovir).	? Infection, increased ferritin from blood transfusion
102037 Letermovir	5	Study drug was stopped on Day 4 due to abnormal LFTs. Subject died on Day 12 due to heart failure, at that time, liver dysfunction was ongoing.	Heart failure, sepsis
100271 Placebo	62	Study drug was discontinued on Day 46 due to CMV viremia, two weeks prior to subject meeting Hy's Law.	GVHD, CMV infection
100334 Placebo	15	Study drug was discontinued on Day 13 due to diarrhea.	Cardiogenic shock, pneumonia with MODS.
100140 Placebo	11	Study drug was discontinued on Day 10 due to LFT abnormalities.	Venoocclusive disease (autopsy-confirmed)

Source: ADDILI dataset and narratives

Reviewer comment: This reviewer has carefully reviewed the 11 cases that fulfilled Hy's Law laboratory criteria and does not believe that any of the cases are likely to represent DILI. Each of the cases has one or more plausible alternative explanations for LFT abnormalities. Additionally, many of the cases had normalization of liver function despite ongoing study drug

exposure and a few cases had ongoing liver dysfunction following discontinuation of the study drug.

Trial P020

Using the same definition of Hy's Law as described for Trial P001, there were a total of 4 subjects who met Hy's Law laboratory criteria in Trial P020: letermovir 60 mg/day, 1(3.0%); letermovir 120 mg/day, 1(3.2%); letermovir 240 mg/day, 1 (2.9%); placebo, 1 (3.0%). The available data for these subjects are presented in the table below. The only subject with a narrative available was subject 104001 who experienced an SAE leading to study drug withdrawal.

Table 54. P020: Subjects Fulfilling Hy's Law Criteria

Patient ID/ Treatment Arm	Study Day Hy's Law Criteria Met	Dechallenge and Rechallenge Results	Alternative Etiology of Liver Abnormalities
104001 Letermovir 60mg	50	Study drug was discontinued on Day 58 due to SAE of liver function tests increased. At the time of discontinuation, the LFTs were already improving.	Cholelithiasis, Liver GVHD, trimethoprim-sulfamethoxazole, amoxicillin, voriconazole
202003 Letermovir 120 mg	43	LFTs intermittently elevated through early treatment period. Study drug was continued through LFT elevation. LFTs normalized by Day 50 despite ongoing study drug.	Amphotericin B, amoxicillin, moxifloxacin, infection
101016 Letermovir 240 mg	43	Study drug was discontinued on Day 11 prior to LFT elevation. Family physician stopped medication due to hypertension, though subject also had CMV viremia around this time.	Liver GVHD, trimethoprim-sulfamethoxazole, voriconazole
201014 Placebo	22	Study drug was discontinued on Day 5 due to AEs (blurring vision and diarrhea). LFTs started increasing around Day 8.	Liver GVHD, voriconazole

Source: JReview Hy's Law plot and graphical patient profiles

Reviewer comment: None of the above 4 cases are strongly suggestive of DILI due to letermovir. The equal distribution of cases across the 4 cohorts (including the placebo arm) also makes it less likely that the events are attributable to letermovir exposure.

8.5.1. Venoocclusive Disease

Venoocclusive disease (VOD) is a well-described complication of HSCT. VOD is thought to be due to obstruction of the small veins in the liver. It typically presents with ascites and hepatic

dysfunction, which may progress to cirrhosis and/or acute liver failure. It most commonly occurs as a result of endothelial damage by a chemotherapeutic agent.

The rate of VOD was noted by the DCRP reviewer to be higher in the letermovir arm (5 (1.3%) vs 0 (0.0%) in the letermovir and placebo arms, respectively). However, it appears that his analysis only included cases with the reported PT 'venoocclusive disease.' There were additional cases of VOD reported as 'venoocclusive liver disease.' When these additional cases are included in the analysis, the rate of treatment-emergent VOD is very similar between arms (7 (1.9%) and 3 (1.6%) in the letermovir and placebo arms, respectively). Serious VOD events occurred in 5 (1.3%) and 3 (1.6%) letermovir and placebo subjects, respectively. Two of the VOD events in each arm were fatal. There were no additional VOD events beyond the treatment period (through Week 48).

8.6. Safety Analyses by Demographic Subgroups

The safety profile of letermovir in key demographic subgroups was examined using the Trial P001 ASaT population.

Age

In Trial P001, the mean (SD) age was similar in the letermovir and placebo arms (50.8 (13.4) years and 50.8 (14.8) years, respectively). Similarly, the proportion of subjects 65 years of age or older was similar in both arms (15.0% and 16.6% in the letermovir and placebo arms, respectively). The table below displays common AEs that occurred at least 2% more frequently in letermovir subjects ≥ 65 years of age compared to letermovir subjects < 65 years of age. Some, but not all, AEs that were more common in older letermovir subjects were also more common in older placebo subjects. AEs that occurred more frequently in older letermovir subjects but did not occur more frequently in older placebo subjects were diarrhea, fatigue, and blood creatinine increased.

Table 55. P001: Common AEs with a ≥ 2% Higher Frequency in Letermovir Subjects ≥ 65 Years of Age Compared to Letermovir Subjects < 65 Years of Age

Preferred Term	Letermovir		Placebo	
	Age < 65 Years N=317 n (%)	Age ≥ 65 Years N=56 n (%)	Age < 65 Years N=160 n (%)	Age ≥ 65 Years N=32 n (%)
Diarrhea	79 (24.9%)	18 (32.1%)	41 (25.6%)	6 (18.8%)
Edema peripheral	43 (13.6%)	11 (19.6%)	13 (8.1%)	5 (15.6%)
Fatigue	40 (12.6%)	10 (17.9%)	18 (11.3%)	3 (9.4%)
Decreased appetite	28 (8.8%)	10 (17.9%)	17 (10.6%)	5 (15.6%)
Acute kidney injury	26 (8.2%)	10 (17.9%)	17 (10.6%)	8 (25.0%)
Blood creatinine increased	29 (9.1%)	7 (12.5%)	13 (8.1%)	0 (0.0%)

Source: ADSL and ADAE dataset

As shown above, both 'acute kidney injury' and 'blood creatinine increased' AEs were more common among letermovir subjects 65 years of age or greater than letermovir subjects less than 65 years of age. A similar trend was observed in placebo subjects. As laboratory results may be more reliable than reported AEs for assessing letermovir's impact on renal function, an analysis of creatinine laboratory toxicity by age was undertaken and is shown in the table below. Notably, the rate of creatinine elevations among subjects less than 65 years of age is only slightly higher in the letermovir arm compared to the rate in the placebo arm. Whereas, among subjects 65 years of age or greater, there is a markedly higher rate of creatinine abnormalities (particularly Grade 4) in letermovir subjects compared to placebo subjects.

Table 56. P001: Creatinine Abnormalities by Age

	Letermovir		Placebo	
Laboratory Parameter	**Age < 65 Years N=317 n (%)**	**Age ≥ 65 Years N=56 n (%)**	**Age < 65 Years N=160 n (%)**	**Age ≥ 65 Years N=32 n (%)**
Creatinine (mg/dL)				
Grade 1 (1.1 to 1.3 x ULN)	3 (1.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
Grade 2 (>1.3 to 1.8 x ULN or increase of >0.3 mg/dL above baseline)	36 (11.4%)	7 (12.5%)	13 (8.1%)	4 (12.5%)
Grade 3 (>1.8 to <3.5 x ULN or increase of 1.5 to <2.0 x baseline)	88 (27.8%)	14 (25.0%)	45 (28.1%)	10 (31.3%)
Grade 4 (≥3.5 x ULN or increase of ≥2.0 x baseline)	58 (18.3%)	17 (30.4%)	28 (17.5%)	3 (9.4%)
Any Grade	185 (58.4%)	36 (69.6%)	86 (53.8%)	17 (53.1%)

Source: ADSL and ADLB datasets

Reviewer Comment: The more marked effect of letermovir on renal function observed among subjects 65 years of age or greater is not surprising as older subjects are known to have increased susceptibility to acute kidney injury of various etiologies. The fact the rate of any Grade creatinine abnormalities was similar among placebo subjects less than and greater than 65 years of age suggests that the higher rate of creatinine abnormalities observed among older letermovir subjects is attributable to letermovir and not to comorbidities and other potentially nephrotoxic drugs.

Given the imbalance in cardiac events observed in the overall safety population, analysis of cardiac events in key demographic subgroups was performed. As was seen in the overall safety population, the rate of cardiac events was higher in the letermovir arm compared to the

placebo arm in both the < 65 years cohort (37/317, 11.7% and 11/160, 6.9% in the letermovir and placebo arms, respectively) and the ≥ 65 years of age cohort (10/56, 17.9% vs 1/32, 3.1% in the letermovir and placebo arms, respectively). However, the difference in the rate of cardiac AEs between the letermovir and placebo arms was more pronounced in the ≥ 65 years of age cohort with a statistically significant risk difference of 14.73 (3.03, 26.44).

Reviewer Comment: It is not unexpected that some AEs, including cardiac AEs, were more common in older subjects. These subjects may be more frail and may be more likely to have comorbidities that predispose them to certain AEs. Therefore, advanced age may be augmenting the cardiac signal detected in the overall population.

Gender

Women made up just less than half of the letermovir arm (211/373, 43.4%). This is considered to be an adequate number of women exposed to the recommended dose and duration of letermovir to allow for assessment of any safe signals that may be unique to women.

In an analysis of all treatment-emergent AEs regardless of severity, nearly 100% of men and women in both arms experienced one or more AE. Common treatment-emergent AEs that occurred with a ≥ 3% difference between men and women in the letermovir arm are presented in the table below. Events that were more common in women were nausea, vomiting, cough, and erythema. Most of these events were not found to be more common in women in the placebo arm. Similarly, there were AEs that were more common in men in the letermovir arm but were not more common in men in the placebo arm (e.g. peripheral edema, acute kidney injury). The etiology and clinical meaningfulness of these differences between men and women are unclear.

Table 57. P001: Common AEs that Occurred with a ≥ 3% Difference Between Sexes in the Letermovir Arm

Preferred Term	Letermovir		Placebo	
	Female N=162 n (%)	Male N=211 n (%)	Female N=76 n (%)	Male N=116 n (%)
Diarrhea	39 (24.1%)	58 (27.5%)	15 (19.7%)	32 (27.6%)
Nausea	47 (29.0%)	52 (24.6%)	18 (23.7%)	27 (23.3%)
Pyrexia	29 (17.9%)	48 (22.7%)	15 (19.7%)	28 (24.1%)
Vomiting	36 (22.2%)	33 (15.6%)	14 (18.4%)	12 (10.3%)
Cough	30 (18.5%)	23 (10.9%)	5 (6.6%)	15 (12.9%)
Edema peripheral	18 (11.1%)	36 (17.1%)	9 (11.8%)	9 (7.8%)
Acute kidney injury	11 (6.8%)	25 (11.8%)	12 (15.8%)	13 (11.2%)
Insomnia	11 (6.8%)	23 (10.9%)	4 (5.3%)	6 (5.2%)

Erythema	19 (11.7%)	14 (6.6%)	3 (3.9%)	8 (6.9%)
Dyspnea	8 (4.9%)	22 (10.4%)	2 (2.6%)	4 (3.4%)

Source: ADSL and ADAE datasets

An additional analysis was performed to assess the rate of cardiac AEs by gender. In the letermovir arm, the rate of cardiac AEs was similar in men and women (12.3% and 13.0%, respectively). Therefore, men and women appear to have both contributed to the overall increase in cardiac events reported in the letermovir arm.

Race

Trial P001 consisted primarily of white subjects (80.7% of the letermovir arm was White) (see Table 5). Black patients were particularly poorly represented (8 Black subjects in the letermovir arm and 4 Black subjects in the placebo arm). Given the small number of subjects in each of the other races, differences in safety within the letermovir cohort by race are not able to be detected.

Reviewer Comment: It is anticipated that a PMC will be issued to obtain additional information regarding the efficacy and safety of letermovir among Black patients.

The safety profile of letermovir in Asian subjects is of particular interest, given the increased letermovir exposure reported in Japanese subjects in Phase 1 trials. In P001, the rate of SAEs was lower among the 40 Asian subjects receiving letermovir (17.5%) compared to the other individual races (40.9% - 75.0%) and compared to the overall letermovir safety population (43.7%). The most common AEs (non-serious) are shown in the table below. The only event that was notably more common in Asian letermovir subjects compared to non-Asian letermovir subjects was rash.

Table 58. P001: Common AEs in Asian and Non-Asian Subjects

Preferred Term	**Letermovir**		**Placebo**	
	Asian N=40 n (%)	**Non-Asian N=333 n (%)**	**Asian N=18 n (%)**	**Non-Asian N=174 n (%)**
Graft versus host disease	16 (40.0%)	130 (39.0%)	9 (50.0%)	64 (36.8%)
Diarrhea	5 (12.5%)	92 (27.6%)	1 (5.6%)	46 (26.4%)
Nausea	9 (22.5%)	90 (27.0%)	2 (11.1%)	43 (24.7%)
Pyrexia	7 (17.5%)	70 (21.0%)	2 (11.1%)	41 (26.6%)
Cytomegalovirus infection	2 (5.0%)	28 (8.4%)	10 (55.6%)	78 (44.8%)
Rash	12 (30.0%)	64 (19.2%)	3 (16.7%)	38 (21.8%)
Vomiting	3 (7.5%)	66 (19.8%)	2 (11.1%)	24 (13.8%)

Cough	1 (2.5%)	52 (15.6%)	2 (11.1%)	18 (10.3%)
Edema peripheral	3 (7.5%)	51 (15.3%)	0 (0.0%)	18 (10.3%)
Fatigue	1 (2.5%)	49 (14.7%)	1 (5.6%)	20 (11.5%)
Headache	3 (7.5%)	49 (14.7%)	2 (11.1%)	16 (9.2%)
Mucosal inflammation	3 (7.5%)	43 (12.9%)	3 (16.7%)	20 (11.5%)
Abdominal pain	5 (12.5%)	39 (11.7%)	0 (0.0%)	18 (10.3%)

Source: ADSL and ADAE datasets

Reviewer Comment: Given the relatively small number of Asian subjects enrolled in P001, it is not clear that the SAE rate in Asian subjects is truly lower than the SAE rate in other races. However, the available data do not suggest that increased drug exposure among Asian subjects is associated with an increase in SAEs in this subpopulation. The significance of the observed increased rate of rash among Asian subjects is unclear. Data from future trials regarding the rate of rash and other AEs among Asian subjects will be of interest.

8.7. Specific Safety Studies/Clinical Trials

No additional trials have been conducted to evaluate specific safety concerns.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Given the relatively short duration of treatment (maximum of 14 weeks) and follow-up (34 weeks) in letermovir clinical trials, assessment for oncologic events is limited. Further, the majority of subjects in the Phase 2b and 3 trials had a history of malignancy and many received chemotherapeutic agents that have been associated with the development of secondary malignancies. Through Week 48, the proportion of subjects experiencing an event within the SOC of Neoplasms, Benign, Malignant, and Unspecified was nearly identical in each arm (18.5% and 18.8% in the letermovir and placebo arms, respectively) and predominantly consisted of subjects experiencing relapse of their underlying disease.

8.8.2. Human Reproduction and Pregnancy

Females who were pregnant were excluded from all clinical trials. Additionally, all subjects of reproductive potential in Trial P001 were required to use or have their partner use 2 acceptable forms of contraception from the time of informed consent through 90 days after the last dose of study drug (slightly different contraception requirements were in place for other clinical trials). There were no pregnancies in the Phase 2 or 3 development program. However, there were two pregnancies in the Phase 1 thorough QT/QTc study. Subject 0016 became aware that she was pregnant after receiving a single dose of moxifloxacin only and subject 0011 confirmed that she was pregnant approximately 14 days after the last dose of study drug. Both pregnancies ended in elective abortion.

As previously noted, based on preclinical findings there has been concern regarding the potential of letermovir to impair male fertility. There were no AEs of 'infertility' reported, however several letermovir subjects experienced the AE testosterone decreased. Please see Section 8.5.5 for a detailed discussion of testicular toxicity.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric studies have not yet been initiated, therefore, no pediatric data are available for review with this application. Additionally, letermovir has orphan drug status and is therefore exempt from Pediatric Research Equity Act (PREA) requirements. (b) (4)

(b) (4)

Reviewer Comment (b) (4)

This was conveyed to the Applicant at the pre-NDA meeting.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In Trial P001, overdose was a pre-specified event of clinical interest, defined as any dose higher than two times the protocol-specified treatment dose. No overdoses and no reports of abuse occurred in the clinical development program for letermovir. Based on letermovir's mechanism of action, no withdrawal or rebound effects are anticipated.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience with letermovir as it is not available on the U.S. market or any foreign market.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety conclusions in this review are primarily based upon data from a single Phase 3 trial. Routine pharmacovigilance activities will be ongoing to detect any potential new safety signals.

8.10. Additional Safety Issues From Other Disciplines

All safety issues from other disciplines have been incorporated into relevant sections elsewhere in this review.

8.11. Integrated Assessment of Safety

The overall safety database for letermovir comes from Trials P020 and P001 and is considered adequate. The IV letermovir safety database comes from Trial P001. The number of subjects exposed to IV letermovir is low and the duration of exposure was short. Therefore, it is anticipated that based on the currently available IV letermovir safety database, a recommendation to limit the use of IV letermovir to instances when oral therapy is not tolerated will be included in labeling. The safety findings from P001 and P020 are described in detail in Sections 8.4 and 8.5, respectively. Safety signals identified in these trials are summarized below. Given the small number of subjects and the use of a letermovir dose that is less than the to-be-marketed dose, the findings from Trial P020 carry less weight than findings from Trial P001.

The following events all occurred in a greater proportion (≥ 2% higher) of subjects receiving letermovir compared to placebo in Trial P001:

- Events under the Cardiac disorders system organ class
- Events under the Ear and labyrinth system organ class- predominantly vertigo and ear pain/discomfort
- Events under the Infection and infestation system organ class after CMV-related events are excluded
- Laboratory evidence of thrombocytopenia (specifically Grade 4) without associated serious bleeding events
- Laboratory evidence of anemia
- Laboratory evidence of renal dysfunction without an associated increase in renal AEs
- Nausea
- Diarrhea
- Vomiting
- Peripheral edema
- Cough
- Headache
- Fatigue
- Abdominal pain

Of the above listed safety signals, the following signals were supported to varying degrees by findings in Trial P020: thrombocytopenia, renal dysfunction, diarrhea, vomiting, peripheral

edema, cough, and headache. For the other events, the findings in Trial P020 were either inconclusive or not suggestive of a signal. It is anticipated that all of the above listed events will be included in the letermovir package insert.

The cardiac safety signal was more pronounced than the other signals and has potentially more serious implications. Therefore, this signal was explored in great detail with the help of a consultation from DCRP. The majority of the reported cardiac events were mild to moderate tachyarrhythmias. There were also a few serious and fatal heart failure events reported, though these events were evenly distributed across the arms. Overall, death due to cardiovascular events was very uncommon in both arms. There was no apparent cardiac safety signal in Trial P020. Many of the cardiovascular AEs in Trial P001 were confounded by the use of other cardiotoxic medications and pre-existing cardiac conditions. Nonetheless, a drug-effect leading to these events cannot be excluded. Therefore, this reviewer believes that a description of the reported cardiac events should be included in the letermovir label, but that these events should not preclude approval of letermovir.

The other safety consideration that was closely scrutinized by this reviewer and by the clinical pharmacology reviewers is the potential for an increase in AEs due to the increase in letermovir exposure following IV administration. As no subjects in Trial P020 received IV letermovir, this assessment relies solely on the findings from Trial P001. As described in Section 8.5.1, there are several AEs that occurred more often during receipt of IV letermovir compared to IV placebo (diarrhea, hypokalemia, fluid overload, hyperglycemia, cough, and edema peripheral). All of these events except for hypokalemia and hyperglycemia were also more common in the overall letermovir arm compared to the overall placebo arm. Review of laboratory values shows that potassium levels were comparable in the IV letermovir and IV placebo arms. However, there is higher proportion of subjects in the IV letermovir arm with elevated glucose levels.
In addition, IV letermovir appeared to be associated with a decline in renal function based on serum creatinine measurements. Combining all grade changes in creatinine, increase in serum creatinine was more common among subjects receiving 7 or more consecutive days of IV letermovir compared to IV placebo. This is of particular interest given the known nephrotoxicity of the cyclodextrin excipient in the IV letermovir formulation. However, the finding is of unclear etiology as a similar trend towards increased serum creatinine in the letermovir arm was also noted among subjects who received only oral therapy.

Extensive exposure-safety analyses were performed by the Applicant using a subset of letermovir subjects in Trial P001 who underwent intensive pharmacokinetic sampling (n = 75). These analyses revealed an association between the letermovir C_{max} and cardiac disorders, arrhythmias, fluid overload, and renal failure (the renal failure association was observed only among subjects receiving 1 or more doses of IV therapy). As noted previously, the analysis of renal failure events among subjects who received 1 or more doses of IV therapy is not considered to be reliable. Also of note, the association between the letermovir C_{max} and cardiac

disorders was based on a system organ class (SOC) analysis. Assessment of the impact of letermovir exposure on events in the cardiac SMQ did not identify an association. No associations between the letermovir AUC and any of the studied AEs were detected.

In addition to performing an exposure – safety analysis of selected AEs, upon request, the Applicant also looked for a potential exposure dependent change in blood urea nitrogen (BUN), creatinine, potassium, and platelet laboratory values. No significant associations between the letermovir AUC or C_{max} and changes in these laboratory parameters were detected.

It should be noted that the exposure-safety analyses were limited by fact that Cmax was not reliably estimated in the population PK model (and all observed associations were with C_{max}) and by the inability to account for subjects' baseline characteristics. Please see the Clinical Pharmacology Review by Dr. Mario Sampson, PhD, for additional details.

According to the Applicant's summary of clinical safety, letermovir was well-tolerated in Phase 1 trials. Among 630 subjects who received letermovir alone or in combination with another drug in Phase 1 trials, 356 (56.5%) of subjects experienced an AE and 253 (40.2%) of these were assessed by the investigator as related to study medication. Eight (1.3%) subjects had letermovir discontinued due to AEs. There were only 2 (0.3%) subjects with reported SAEs and there were no deaths. The SAEs included a urinary tract infection with prostatitis in a subject receiving letermovir 40 mg BID x 3 doses and peripheral ischemia in a subject with severe renal impairment, 7 days after completing treatment with letermovir 120 mg daily.

Similarly, letermovir was well tolerated in the Phase 2a trial, P019. In this trial, subjects received letermovir 80 mg daily for a maximum of 14 days. Among 27 subjects, 20 (74.1%) experienced one or more treatment-emergent AEs. The most common AEs were urinary tract infection, hypertension, and nasopharyngitis. Three (11.4%) subjects experienced 4 SAEs (abnormal feces, renal disorder, arteriovenous fistula aneurysm, and renal lymphocele) and one of these subjects was in the standard of care arm. There were no deaths.

Reviewer Comment: There are no concerning safety findings in the Phase 1 trials or the Phase 2a trial.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee or other external consultations were held to discuss this application.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations with the Applicant are ongoing. Below are general clinical recommendations for proposed labeling. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted.

Indications and Usage

- The Applicant has proposed the following indication: *TRADEMARK is indicated for prophylaxis of cytomegalovirus(CMV) infection or disease in adult CMV-seropositive recipients [R+] of allogeneic hematopoietic stem cell transplant (HSCT).*
- As (b) (4) *TRADEMARK is indicated for prophylaxis of cytomegalovirus (CMV) infection in adult CMV-seropositive recipients [R+] of allogeneic hematopoietic stem cell transplant (HSCT).* A definitive conclusion has not been reached at this time, and any changes to the indication will have to be negotiated with the Applicant.

Dosage and Administration

- Add a Section 2.2: **Testing Before and During Treatment**. In this section, prescribers will be advised to monitor patient's renal function on a regular basis during treatment with letermovir.
- Add the following statement to the **Recommended Dosage in Adult Patients** Section: TRADEMARK injection should only be given to subjects unable to take oral therapy and patients should be switched to oral TRADEMARK as soon as the injection is no longer necessary.
- The section on **Renal Impairment** will be modified to reflect the potential for hydroxypropyl-β-cyclodextrin, the intravenous vehicle of TRADEMARK, to accumulate in the setting of renal impairment.
- Discussions are currently ongoing regarding the most appropriate recommendation for use in subjects with hepatic impairment.

Contraindications

- We agree with the Applicant's proposal to contraindicate TRADEMARK in patients receiving pimozide and ergot alkaloids due to the strong potential for serious adverse events due to drug-drug interactions.

Warnings and Precautions

- Remove "The concomitant use of TRADEMARK and certain rugs may result in (b) (4) potentially significant drug interactions…." from this section.
- At the time of this review, it has not been determined if the increased rate of cardiac events in TRADEMARK subjects compared to letermovir subjects necessitates a warning.

Adverse Reactions: Clinical Trials Experience

- Only safety data from Trial P001 will be presented.
- Adverse events occurring in at least a 2% higher proportion of letermovir subjects than placebo subjects will be included in the label as adverse reactions (ARs). Common ARs to be included are: nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, and abdominal pain.
- The higher rate of cardiac events will be described.
- The higher rate of infection events may be included, pending further discussions with the Applicant.
- A table showing hemoglobin, absolute neutrophil count, platelet count, and creatinine graded toxicities will be included.

Clinical Studies

- Only P001 results will be presented.
- The rate of on-treatment failure (i.e., breakthrough viremia) in the letermovir arm will be presented Section 14.
- It is anticipated that the (b) (4) will be removed.
- The all-cause mortality rates reported by the Applicant do not include the additional deaths that occurred after study discontinuation but before Week 48. The Kaplan-Meier event rate for all-cause mortality will be revised to include these additional deaths.
- (b) (4) will be removed from the label.

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the Package Insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

No issues were identified to necessitate REMS.

12 Postmarketing Requirements and Commitment

The following post-marketing studies are currently under consideration as Post-Marketing Requirements (PMRs) or Post-Marketing Commitments (PMCs):

- CMV prophylaxis trial in renal transplant recipients (letermovir vs. valganciclovir; trial P002 already proposed)
- CMV prophylaxis trial comparing 100 days vs. 200 days of letermovir in HSCT recipients

- In vitro study evaluating the induction of CYP2C8 by letermovir
- A study to determine the phenotypes of substitutions that emerged in virologic failures in TrialP001.

Additional data are also needed regarding the safety and efficacy of letermovir in the following patient subgroups: subjects receiving IV letermovir, Black subjects, and Hispanic subjects. It is anticipated that additional data from each of these populations will be obtained from the postmarketing trials outlined above.

13 Appendices

13.1. References

1. Ljungman, P., M. Hakki, and M. Boeckh, *Cytomegalovirus in hematopoietic stem cell transplant recipients.* Hematol Oncol Clin North Am, 2011. **25**(1): p. 151-69.
2. Reed, E.C., et al., *Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants.* Ann Intern Med, 1988. **109**(10): p. 783-8.
3. Razonable, R., *Direct and indirect effects of cytomegalovirus: can we prevent them?* Enferm Infecc Microbiol Clin, 2010. **28**(1): p. 1-5.
4. Zaia, J.A., *Prevention of cytomegalovirus disease in hematopoietic stem cell transplantation.* Clin Infect Dis, 2002. **35**(8): p. 999-1004.
5. Boeckh, M. and P. Ljungman, *How we treat cytomegalovirus in hematopoietic cell transplant recipients.* Blood, 2009. **113**(23): p. 5711-9.

6. Ljungman, P., P. Griffiths, and C. Paya, *Definitions of cytomegalovirus infection and disease in transplant recipients.* Clin Infect Dis, 2002. **34**(8): p. 1094-7.
7. Webster, A.C., et al., *Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials.* Transplantation, 2006. **81**(9): p. 1234-48.
8. Ljungman, P., et al., *Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials.* Clin Infect Dis, 2017. **64**(1): p. 87-91.
9. Cantoni, N., et al., *Evidence for a bidirectional relationship between cytomegalovirus replication and acute graft-versus-host disease.* Biol Blood Marrow Transplant, 2010. **16**(9): p. 1309-14.
10. Salzberger, B., et al., *Neutropenia in allogeneic marrow transplant recipients receiving ganciclovir for prevention of cytomegalovirus disease: risk factors and outcome.* Blood, 1997. **90**(6): p. 2502-8.
11. Humar, A., et al., *Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study.* Transplantation, 2010. **90**(12): p. 1427-31.
12. Pietersma, F.L., et al., *Influence of donor cytomegalovirus (CMV) status on severity of viral reactivation after allogeneic stem cell transplantation in CMV-seropositive recipients.* Clin Infect Dis, 2011. **52**(7): p. e144-8.

13.2. AEs Resulting in Death through Database Lock, Non-Relapse Related (P001 ASaT Population)

Subject	Arm	AE Preferred Term	Day of Fatal AE Onset	Day of Death	Comments
0003-100271	Placebo	GVHD Aspergillus infection	22 161	225	Treatment discontinued Day 46 due to CMV viremia
0004-100162	Placebo	GVHD	11	50	Study drug discontinued on Day 38. Subject developed hypoxemia and respiratory distress the day prior to death.
0012-100134	Letermovir	Fusarium infection	189	247	Subject experienced recurrent ALL on Day 102, for which she received additional chemotherapy and radiation. She had neutropenic fever from Day 141-145. It is not clear if she was neutropenic at the time of

					fusarium infection.
0014-102131	Letermovir	Respiratory failure	13	25	Respiratory failure attributed to aspiration pneumonia
0017-100419	Letermovir	Venoocclusive disease (VOD)	18	37	Subject also had pneumonia with septic shock on Day 31
0017-102137	Placebo	Septic shock	17	18	Septic event associated with enterococcal bacteremia
0017-102139	Letermovir	Respiratory failure	219	249	Treatment discontinued Day 41 due to possible SJS. CMV infection diagnosed on Day 104 (CMV pneumonia per investigator, but not confirmed by CAC). CMV infection resolved by Day 176. At time of respiratory failure, had lower respiratory fluid culture positive for MDRO.
0018-100254	Letermovir	Septic shock	8	10	Subject diagnosed with VOD on Day 6. Had bacteremia and candidemia at time of death.
0018-100255	Letermovir	GVHD	166	192	Subject first diagnosed with serosal GVHD on Day 90, this episode resolved by Day 112. Second episode of GVHD involved skin, liver, and gut and was refractory to treatment.
0018-100258	Letermovir	Septic shock	185	185	Post-transplant course complicated by GVHD of the skin from Day 15-110. Subject self-discontinued study drug on Day 21. Sepsis thought to be due to *Aspergillus* endocarditis.
0018-100401	Letermovir	Acute hepatic failure	21	24	Subject admitted from clinic on Day 21 with increased LFTs thought to be due to GVHD or VOD. Met Hy's Law criteria on Day 22.
0018-100402	Letermovir	Systemic candida	206	246	Study medication discontinued on Day 26 due to vomiting. This resolved on Day 34. On Day 64 she developed

					CMV viremia requiring PET. On Day 179 she was diagnosed with typhlitis.
0018-101960	Placebo	Septic Shock	89	91	Subject presented to ED on Day 89 with abdominal pain and hematochezia. Developed septic shock. No pathogen identified.
0018-102011	Placebo	Chronic kidney disease	131	136	Subject had CMV viremia leading to study treatment discontinuation on Day 62. On Day 128 he developed GVHD of the gut (ongoing at time of death). He had worsening renal function on Day 131 and started HD on Day 133. Autopsy showed CKD and ATN (only autopsy findings provided).
0018-102015	Placebo	Lung disorder	117	144	She had CMV viremia on Day 25 leading to study drug discontinuation. On Day 73, she was diagnosed with GVHD (gut and skin), which resolved by Day 112. Cause of hypoxia/lung disease unknown. Bronchoscopy was negative.
0018-102074	Placebo	Hemorrhage intracranial	220	222	Diagnosed with CMV colitis on Day 204 (confirmed by AC). Was on valganciclovir at time of bleed. No CBC reported.
0018-102108	Placebo	Diffuse alveolar hemorrhage (DAH).	224	253	Post-transplant course was relatively uncomplicated until the development of DAH. The diagnosis was confirmed by open lung biopsy.
0018-102187	Letermovir	Septic shock	95	95	Sepsis likely due to coagulase-negative staphylococcus bacteremia. Subject had received pulse-dose steroids on Day 90 for possible lung GVHD.
0018-102188	Letermovir	GVHD	69	112	Subject's final weeks were complicated by skin and gut GVHD, recurrent AML, *E. coli* and *Rothia*

					mucilaginosa bacteremia.
0019-100111	Letermovir	Pneumonia RSV	278	290	Study drug discontinued on Day 15 due to positive galactomannan and need to achieve effective voriconazole level. She developed CMV viremia and started PET on Day 58.
0020-100029	Letermovir	Pneumonia	21	45	Narrative describes pneumonia as "fungal" in nature. CMV was detected in BAL fluid on Day 28. Plasma CMV PCR was negative at that time and subject was not treated for CMV (likely just viral shedding).
0020-102221	Placebo	Pneumonia staphylococcal	121	123	Subject had low level CMV viremia starting on Day 85. Never reached threshold, but PET (GCV) initiated. Fatal pneumonia was associated with *S. aureus* and *E. faecium* bacteremia. Subject also had gut GVHD that was ongoing at time of death.
0030-100334	Placebo	Cardiogenic shock	14	15	Subject discontinued study drug due to diarrhea at day 7. The cardiogenic shock event was associated with a lobar pneumonia. She developed multiorgan failure, including hepatic dysfunction (met Hy's law criteria on Day 15). CMV DNA was 680 copies/mL on day of death, but had been previously undetectable. No PET was initiated.
0030-101862	Letermovir	GVHD	10	251	GVHD involving gut +/- skin led to study drug discontinuation on day 23. The GVHD was unresolved at time of death. Subject's course was complicated by three episodes of CMV viremia resulting in PET initiation.
0034-100285	Placebo	Pulmonary	76	147	This subject was enrolled at an Italian

		tuberculosis			site. Bone marrow biopsy showed findings potentially consistent with disseminated mycobacterial infection. The subject also experienced CMV viremia leading to study drug discontinuation on Day 29 (resolved by Day 40).
0034-100287	Letermovir	Sepsis	98	111	Events surrounding subject's death are unclear. Narrative describes a nasal culture positive for adenovirus, an intraabdominal abscess, and "embolization of L2 and L3" (unclear meaning) with resultant hemorrhagic shock.
0041-101820	Placebo	Septic shock	17	18	Subject diagnosed with GVHD SAE on Day 11, leading to study drug discontinued on Day 12. Found to have CMV disease on gastric biopsy performed on Day 17 (CAC confirmed). Also on Day 17, had polymicrobial bacteremia (gram negative). Unclear if he ever had GVHD or if it was CMV disease all along.
0041-101822	Letermovir	GVHD	10	46	Subject had skin and gut GVHD refractory to treatment. Study drug was discontinued on Day 17.
0042-100140	Placebo	VOD	10	22	Subject met Hy's law criteria on Day 10. Study drug discontinued on Day 10. Autopsy confirmed VOD as cause of death.
0042-100144	Letermovir	Pneumonia	160	185	Subject was receiving treatment for gut GVHD at time of pneumonia. Subject also had CMV viremia (440 copies/mL) leading to PET starting on Day 145.
0042-101759	Placebo	GVHD	59	98	Subject experienced CMV viremia leading to study drug discontinuation

					and PET initiation on Day 79. CMV viral load was still positive on Day 91 when last checked (737 copies/mL).
0044-101915	Letermovir	GVHD	1	279	Subject completed study drug on Day 67. Subject started PET on Day 100 for CMV DNA below threshold. GVHD remained active up until death. On Day 239 subject was hospitalized with necrotizing *Pseudomonas* pneumonia.
0045-101674	Letermovir	Parainfluenza virus infection	111	197	BAL sample from Day 145 showed *Aspergillus* and parainfluenza.
0058-100129	Letermovir	Clostridium bacteremia	95	102	Study drug discontinued due to cerebral hemorrhage on Day 5. Subject experienced multiple episodes of CMV viremia, first on Day 10. CMV PCR was detected but not quantifiable when last measured on Day 99. Cause of death reported to be *Clostridium* bacteremia. However, narrative describes a patient with nausea and diarrhea and a positive *Clostridium difficile* toxin A and B, suggestive more of *C. difficile* colitis.
0061-101708	Letermovir	Bronchopulmonary aspergillosis	103	125	Diagnosed with GVHD SAE on Day 48, was ongoing at time of death.
0063-100091	Letermovir	Atypical pneumonia	185	198	Subject experienced transplant failure on Day 26 and was re-transplanted on Day 32. Subject received study drug continuously from Day 1 to 95.
0063-100092	Letermovir	Sepsis Bronchopulmonary aspergillosis	3 8	13	BAL culture positive for *Aspergillus fumigatus* and sputum culture positive for *Eschericia coli.*
0063-101713	Letermovir	Sepsis	98	130	Subject had GVHD earlier in post-transplant course (Day 44 to 73). Diagnosed with relapsed CML on Day 111. He subsequently experienced a blast crisis. No source of infection

					identified, death may have been relapse-related.
0064-102005	Placebo	Pneumonia	310	316	Subject developed CMV viremia on Day 16, leading to discontinuation of study drug and initiation of PET. Subject had intermittent viremia up until death. Additionally, CMV detected on BAL. CMV end-organ disease (pneumonia) confirmed by AC.
0069-101621	Placebo	Pneumonia	283	348	Subject first developed CMV viremia on Day 28, study drug was discontinued and PET started on Day 39. CMV infection was considered resolved by Day 57. Very little information available regarding death as it happened at a hospital far from the study site.
0075-101699	Placebo	MODS Sepsis Bronchopulmonary aspergillosis	82 82 76	84	Subject also had mild GVHD from Day 17 through the time of death.
0078-102096	Letermovir	Pneumonia	27	29	No pulmonary pathogen identified. Patient was found to have plasma CMV DNA of 265 copies/mL on Day 1 of study. CMV viral load peaked on Day 8 at 862 and was then undetectable by Day 15. Study drug was continued through this period of CMV viremia. No PET was initiated, but subject was considered a failure.
0091-101745	Letermovir	GVHD	337	384	Subject experienced CMV viremia requiring PET on Day 318.
0100-100116	Letermovir	Gastrointestinal hemorrhage	96	124	Study drug was discontinued on Day 49 due to pancytopenia. Pancytopenia was ongoing at time of death. Bleed thought to be due to

					thrombocytopenia, no GI pathology reported. Subject had CMV viremia starting on Day 91, viral load was undetectable by Day 119. No anti-CMV therapy reported.
0102-101690	Placebo	GVHD	176	243	This was the subject's 2nd episode of GVHD (gut). He also experienced 2 episodes of CMV viremia requiring PET starting on Day 54 and then again on Day 203.
0108-100075	Placebo	GVHD	75	166	Subject experienced CMV viremia leading to study drug discontinuation and PET initiation on Day 33. Peak viral load was 211,565 IU/mL on Day 96. He remained on anti-CMV therapy until the time of death, though his last CMV DNA was DNQ. Subject's non-Hodgkin's lymphoma relapsed on Day 70.
0108-102069	Letermovir	Klebsiella sepsis	61	64	Subject's post-transplant course was also complicated by GVHD and VOD, both of which were ongoing at the time of death. Study drug was discontinued on Day 58 due to VOD.
0116-100044	Letermovir	Respiratory failure	86	92	Subject also experienced GVHD SAE that was considered to be resolving at the time of death. In the weeks leading up to his death, two bronchoscopies were positive for parainfluenza virus.
0116-100048	Letermovir	GVHD	34	178	Gut and skin GVHD were ongoing at time of death.
0116-101663	Letermovir	MODS	149	149	Subject had recurrence of AML on Day 94 and developed GVHD on Day 109. On Day 138 he presented to the ED with pneumonia, in the following days he developed MODS and tumor lysis syndrome. On Day 147 he was

					found to have a CMV DNA of 1586 copies/mL, but was not treated. He was made DNR.
0116-102241	Letermovir	Failure to thrive	39	54	The subject without a history of significant liver disease had progressive liver dysfunction post-transplantation. Hyperbilirubinemia was reported on Day 4, hepatic cirrhosis on Day 10, and encephalopathy on Day 18. Study drug was Discontinued on Day 22 due to progressive encephalopathy. Following letermovir discontinuation, she remained somnolent with stable, low-level hyperbilirubinemia.
0117-100007	Placebo	Sepsis	146	148	On Day 20 study drug was stopped due to CMV viremia and PET was initiated. Subject was diagnosed with recurrent AML on Day 143.
0117-100008	Letermovir	Pneumonia	259	268	Subject developed CMV viremia on Day 44. Study drug was discontinued and PET was initiated. A 2nd episode of CMV viremia occurred on Day 71. The 2nd CMV infection SAE was considered resolved on Day 86, but subject remained viremic until at least Day 239 (last reported value). BAL culture near end of life was positive for CMV. Case was not evaluated by CAC as the event occurred after week 24.
0117-101628	Letermovir	Sepsis	115	116	Subject experienced gut GVHD with onset on Day 100. GVHD was ongoing at time of death. Etiology of sepsis not identified.
0123-100055	Letermovir	Neutropenic sepsis	180	187	Subject had relapsed leukemia (not reported as an AE, but stated in narrative). Chest imaging around time of death was suggestive of

					pneumonia and RSV was detected from an unspecified specimen.
0123-100056	Letermovir	Sepsis	42	56	Subject experienced AML relapse on Day 8, leading to study drug discontinuation on the same day. He had an SAE of diverticulitis from Day 36-39. Then on Day 43 developed sepsis with imaging showing resolving diverticulitis and new lung infiltrates. He developed MOSD and was made comfort care only.
0123-101679	Letermovir	Pneumonia	139	158	Subject had progressive pneumonia. He was transitioned to comfort care on Day 158 and died that same day.
0124-101867	Placebo	GVHD	92	172	Subject developed CMV viremia, leading to PET on Day 36. She had intermittent viremia throughout the study and at time of death CMV infection was considered ongoing. On Day 92 she developed diarrhea and colonoscopy biopsy findings were consistent with GVHD (no mention of CMV stains). He had a prolonged hospitalization for Grade 4 GVHD and was placed in hospice care on Day 170.
0129-102234	Placebo	GVHD Cardiac arrest	123 189	189	Subject was 56 years old and had no reported cardiac history. On Day 123 the he was diagnosed with GI GVHD. The GVHD was refractory and the treatment course was complicated by sepsis and CMV viremia (Days 143 and 165). He first had a cardiac arrest on Day 189 with eventual return of circulation. A second arrest occurred on Day 189 and was fatal.
0131-101833	Letermovir	Pneumonia	202	211	Subject was reported to have recurrent AML on Day 155, which was then reported as resolved on Day 167.

					She subsequently developed pneumonia and organ failure, leading to death. It is not clear how relapsed leukemia could resolve so quickly. Perhaps this was reported in error?
0131-101834	Placebo	Bacterial sepsis	14	17	Subject developed gram-negative sepsis on Day 14. Study drug was withdrawn on Day 15.
0131-101954	Letermovir	Thrombocytopenia	**-2**	11	A 55 year-old subject with myelodysplastic syndrome and no cardiac history. She experienced an SAE of thrombocytopenia from Day -2 to 11 and an AE of bacteremia from Day -3 to Day 11. Study drug was discontinued on Day 9 due to the thrombocytopenia. She was started on dialysis on Day 8 and mechanical ventilation on Day 10. The subject died following a cardiac arrest on Day 11. The investigator cited thrombocytopenia as the cause of death, though there is no description of a bleeding event. The provided narrative is more suggestive of a sepsis-related death.
0131-101981	Letermovir	Mucormycosis Pancreatitis Hypokalemia	187 189 209	227	This subject was 65 without reported cardiac history. First episode of mucormycosis of the sinuses occurred from Day 62-157. Mucormycosis with cranial involvement was reported on Day 187. While she was being treated for the fungal infection, she developed pancreatitis and hypokalemia and died of cardiac arrest on Day 227.
0140-101801	Letermovir	GVHD	202	255	Very little information provided regarding GVHD and events surrounding death.

0140-102024	Letermovir	Pneumonia	84	129	Subject was diagnosed with GVHD on Day 21 and on Day 32 he was diagnosed with CMV colitis (confirmed by CAC). Both CMV and GVHD were ongoing at time of death.
0142-102001	Placebo	Immune thrombocytopenic purpura (ITP)	83	97	Subject had completed study drug on Day 72. Diagnosis of ITP based on presence of anti-platelet antibodies. She experienced an intracerebral hemorrhage on Day 90 that was ultimately fatal.
0142-102003	Placebo	Pneumonia bacterial	85	99	Subject developed GVHD on Day 44 and CMV viremia on Day 64. Both of these events were considered resolved when the subject developed *Klebsiella* pneumonia.
0147-100019	Placebo	MODS	151	155	Subject had mild GVHD starting on Day 9, ongoing at time of death. Had CMV viremia starting on Day 26, leading to study drug discontinuation and initiation of ganciclovir. On Day 42 subject was switched to foscarnet and then developed renal failure on Day 54. Patient continued to have intermittent CMV viremia up until time of death (on ganciclovir through Day 152). Minimal details regarding the event of MODS are provided.
0147-100020	Letermovir	Septic shock	15	23	Subject had mild GVHD starting on Day 1. Source of sepsis not identified.
0147-100023	Placebo	Pneumocystis jirovecii pneumonia (PJP)	86	93	Subject had CMV viremia on Days 86 and 93 (155 and 2130 copies/mL, respectively), but does not appear to have been starting on CMV therapy. She died at home of respiratory failure on the same day she was discharged from hospitalization for PJP.

0148-100206	Placebo	MODS	172	191	Subject had CMV viremia on Day 36 and study drug was discontinued. She had intermittent viremia throughout the study. When last reported (Day 153) her CMV viral load was 2009 copies/mL and she was on foscarnet at the time of death. Etiology of MODS not reported.
0164-102037	Letermovir	Cardiac Failure	2	12	Subject had a history of chronic heart failure and had progression of his heart failure early on in study. He subsequently developed hepatic dysfunction that was attributed to the heart failure.
0175-101890	Letermovir	Bacteremia	285	292	Subject experienced CMV viremia starting on Day 124, with a peak viral load of 23,106 copies/mL on Day 138. At time of death, CMV DNA was DNQ. Subject was on valganciclovir through Day 291. Bacteremia associated with neutropenic fever.

Source: Subject Narratives
Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ATN, acute tubular necrosis; BAL, bronchoalveolar lavage; CKD, chronic kidney disease; CAC, clinical adjudication committee; DNQ, detected not quantifiable; DNR, do not resuscitate; ED, emergency department; GCV, ganciclovir; GVHD, graft versus host disease; HD, hemodialysis; MODS, multiple organ dysfunction syndrome; MDRO, multidrug resistant organism; PET, pre-emptive therapy; RSV, respiratory syncytial virus; SJS, Stevens-Johnson syndrome; VOD, venoocclusive disease

13.3. Financial Disclosure

There were no financial disclosures of significant concern. The financial disclosures as described in this section do not affect the approvability of letermovir.

Covered Clinical Study (Name and/or Number): P001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 507		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1 (Investigator's spouse was a Merck employee)*		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1*		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

(b) (6)

Reviewer Comment: Based on the randomized, blinded trial design, the potential for (b) (4) *financial interests to bias the trial results is negligible.*

Covered Clinical Study (Name and/or Number): P020

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 114		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant) – Not Applicable
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)- Not Applicable
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)- Not Applicable

There were no investigators with disclosable financial interests which could potentially bias this trial.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AIMEE C HODOWANEC
08/07/2017

ANDREAS PIKIS
08/07/2017