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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 11, 2017
From	Andreas Pikis
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 209939 & NDA 209940
Applicant	Merck Sharp & Dohme Corp
Date of Submission	March 8, 2017
PDUFA Goal Date	November 8, 2017
Proprietary Name / Non-Proprietary Name	PREVYMIS/letermovir
Dosage form(s) / Strength(s)	Tablets: 240 mg and 480 mg Injection: 240 mg/12 mL and 480 mg/24 mL
Applicant Proposed Indication(s)/Population(s)	Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic HSCT

1. Benefit-Risk Assessment

I am in agreement with the Risk-Benefit Assessment as provided in the Clinical Review by Dr. Aimee Hodowanec. Therefore, this section closely mirrors that found in the Clinical Review with the exception of relatively minor revisions that do not substantively impact the overall Risk-Benefit Assessment.

Benefit-Risk Summary and Assessment

Cytomegalovirus (CMV) is a serious life-threatening infection in immunocompromised patients. This is particularly true for allogeneic hematopoietic cell transplant (HSCT) recipients. Because of the increased morbidity and mortality associated with CMV infection, it has been recognized that prevention of CMV disease may be a better strategy than a treatment of an established CMV infection. Prophylactic therapy (treatment administered to all patients at risk for developing CMV disease) and preemptive therapy (treatment of patients with evidence of CMV replication in the blood) are the two major strategies used for prevention of CMV disease in HSCT recipients. Although prophylaxis is the preferred strategy in high risk solid organ transplant (SOT) recipients, preemptive therapy is the preferred strategy in HSCT recipients. Despite demonstrated a decreased incidence of CMV infection, prophylaxis trials in HSCT patients with currently available drugs were associated with increased incidence of bacterial and fungal infections due to the myelosuppression caused by these drugs. Therefore, the standard of care for the treatment of CMV infection or disease in these patients is typically intravenous administration of ganciclovir or its oral prodrug valganciclovir. The use of intravenous foscarnet or cidofovir is limited to patients who are resistant or intolerant to ganciclovir/valganciclovir. Given the toxicities of available drugs as well as the indirect effects of CMV infection, it is preferable to prevent rather than to treat CMV viremia. Clearly, there is an urgent need for effective and safe anti-CMV drugs for prophylaxis in HSCT recipients.

Letermovir is a first-in-class inhibitor of the CMV DNA terminase complex which is involved in viral DNA cleavage and packaging. In this submission, the Applicant seeks approval of letermovir for CMV prophylaxis in allogeneic HSCT recipients with the hope to fulfill this unmet medical need.

In the pivotal phase 3 trial(P001), letermovir administered prophylactically for 14 weeks after HSCT demonstrated superiority over placebo in preventing clinically significant CMV infection through Week 24 post-transplantation ($p < 0.001$). Clinically significant CMV infection was defined as onset of CMV disease or initiation of anti-CMV preemptive therapy (PET) based on documented CMV viremia at levels above a prespecified threshold. The primary endpoint was met primarily by preventing CMV viremia. CMV end-organ disease was very uncommon in both arms given the close CMV PCR monitoring and initiation of PET following detection of CMV viremia. In addition to meeting the primary endpoint, letermovir was shown to provide a survival benefit through week 24 post-transplant, and through week 48

post-transplant, although the difference in mortality was statistically significant only at the 24 week time point.

Cardiac adverse events were the major difference between subjects who received letermovir and placebo (13% vs 6%). The most common cardiac adverse events were tachycardia (in 4% of letermovir subjects and in 2% of placebo subjects) and atrial fibrillation (in 4% of letermovir subjects and in 1% of placebo subjects). Most of these events were considered mild or moderate in severity. Most of these events were also confounded by pre-existing medical conditions and the use of other cardiotoxic medications and they were not considered related to study drug.

In conclusion, approval of letermovir for CMV prophylaxis in adult allogeneic CMV-seropositive HSCT recipients is fully supported by the provided efficacy and safety data submitted with this application. Based on the accumulated clinical literature supporting that CMV viremia predicts CMV disease, this reviewer recommends letermovir for traditional approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cytomegalovirus is the most frequent pathogen in HSCT recipients, contributing significantly to both patient morbidity and mortality. • HSCT CMV seropositive patients are at higher risk for development of CMV infection. • Approximately 27,000 allogeneic HSCTs are performed every year. It is estimated that 65-80% of these patients are CMV seropositive.	CMV is a significant cause of morbidity and mortality in allogeneic HSCT recipients.
Current Treatment Options	• Two strategies have been adopted for the prevention of CMV infection and/or disease in HSCT recipients: o Prophylaxis: treatment is administered to all patients at risk for CMV disease o Preemptive therapy: treatment of patients with evidence of CMV replication in the blood • No drug is approved for CMV prophylaxis in HSCT recipients • Although prophylaxis is the preferred strategy in solid organ transplant patients, it remains unpopular in HSCT recipients because of the treatment-related adverse effects associated with currently available drugs (myelosuppression with subsequent bacterial and fungal infections).	There is an urgent need for new effective and less toxic anti-CMV drugs that could be administered prophylactically in HSCT recipients.
Benefit	• The efficacy of letermovir was established in one Phase 3 trial (P001) and supported by one phase 2 trial (P020). • The primary endpoint in Trial P001 was the proportion of subjects with clinically significant CMV infection through Week 24 after HSCT. This was defined as onset of	One phase 3 trial provided substantial evidence that letermovir administered prophylactically in HSCT

CMV disease or initiation of anti-CMV preemptive therapy (PET) based on documented CMV viremia. The results are shown below:

Efficacy parameter	**Letermovir N=325**	**Placebo N=170**	***P* value**
Clinically significant CMV infection by Week 24	57 (18%)	71 (42%)	<0.001
Initiation of PET	52 (16%)	68 (40%)	
CMV end-organ disease	5 (2%)	3 (2%)	

- The efficacy was supported by the results of a phase 2b dose ranging study (P020) despite the fact that the drug doses used in this study were lower than the recommended clinical dose. A dose-response was established in this trial where all letermovir doses resulted in less CMV prophylaxis failure than placebo. The primary endpoint in this trial was defined as the development of CMV replication in the blood and/or CMV end-organ disease through Day 84 (on-treatment).

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)	0.5 (0.2, 1.6)	0.3 (0.1, 0.9)	0.2 (0.1, 0.7)	Reference
p-value	0.321	0.014	0.007	Reference

recipients significantly reduces the incidence of clinically significant CMV infection through Week 24 post-transplantation.

The primary end-point was driven by the incidence of CMV viremia. CMV end-organ disease was very uncommon given the close CMVmonitoring and initiation of PET following detection of CMV viremia.

Risk

- The safety database for letermovir is primarily based on the phase 3 trial (P001) which includes a total of 565 patients: 373 patients in the letermovir arm and 192 in the placebo arm (all subjects as treated population). Considering that CMV disease is serious and life-threatening in HSCT recipients and that letermovir has received orphan drug designation, a safety database of more than 300 patients who received the proposed dose and duration is considered adequate.
- Nausea, diarrhea, pyrexia, and rash were the most commonly reported adverse events (> 20%) and occurred at a similar rate as in the placebo arm.
- Cardiac adverse events constituted the major difference in adverse events in subjects

Letermovir demonstrated an overall favorable safety profile.

	who received letermovir and placebo (13% vs 6%). The most common adverse events were tachycardia (in 4% of letermovir subjects and in 2% of placebo subjects) and atrial fibrillation (in 4% of letermovir subjects and in 1% of placebo subjects). Most of these events were mild or moderate in severity. These events were also confounded by pre-existing medical conditions and the use of other cardiotoxic medications and all were considered by the investigators as not related to study drug. • Only 72 patients received intravenous letermovir for 7 or more consecutive days. The safety profile of these patients was similar to those who received oral letermovir. The most significant difference was the incidence of hyperglycemia (in 7% of patients who received intravenous formulation versus 4% in those who received oral formulation). This was probably due to the 5% dextrose that is often used to dilute the intravenous letermovir.	
Risk Management	• The Applicant conducted numerous drug-drug interaction studies to characterize the impact of letermovir on concomitant medications and vice versa.	Product label adequately addresses drug-drug interactions with recommendations on how to avoid or on how to manage interactions.

2. Background

Cytomegalovirus is the most frequent pathogen in transplant recipients, contributing significantly to both patient morbidity and mortality. The incidence of CMV infection and disease in transplant patients depends on different factors such as transplant type, donor and recipient CMV serostatus and the level of immunosuppression. Among HSCT recipients, CMV seropositive patients are at the highest risk for development of CMV infection. Without intervention, approximately 70% to 80% of CMV seropositive HSCT recipients will experience CMV infection (viremia) and approximately 30 percent of the patients with CMV viremia will develop tissue invasive CMV disease. CMV pneumonia is the most common and serious manifestation of CMV infection associated with high mortality rate.

Because of the increased morbidity and mortality associated with CMV infection, it has been recognized that prevention of CMV disease may be a better strategy than treatment of established CMV disease. Two strategies have been adopted for the prevention of CMV disease; prophylactic therapy (treatment administered to all patients at risk for developing CMV disease) and preemptive therapy (treatment of patients with evidence of CMV replication in the blood). Although prophylaxis is the preferred strategy in SOT recipients, it remains unpopular in HSCT patients. Despite decreasing CMV infection, prophylaxis trials in HSCT patients with currently available drugs were associated with bacterial and fungal infections because of the neutropenia caused by these drugs. Therefore, preemptive therapy is currently the preferred strategy for the treatment of CMV infection in HSCT recipients. The typical standard of care in these patients is the intravenous use of ganciclovir or its oral prodrug valganciclovir in patients with evidence of CMV replication. The intravenous use of foscarnet or cidofovir is limited to patients who are resistant or intolerant to ganciclovir/ valganciclovir. Clearly, it is preferable to prevent rather than to treat CMV infection in these patients considering the toxic adverse reactions associated with these drugs and the indirect effects of CMV infection. These factors support the need for development of new anti-CMV drugs that are effective and less toxic and can be used for prophylaxis in HSCT recipients.

Currently, there are only four drugs approved by the FDA for the systemic treatment of CMV disease, but none of them is approved for prophylaxis in HSCT recipients: ganciclovir and its prodrug valganciclovir, foscarnet, and cidofovir. Ganciclovir in its intravenous formulation was the first antiviral drug approved by FDA for the prevention of CMV disease in adult transplant recipients. Intravenous ganciclovir is also approved for the treatment of CMV retinitis in immunocompromised patients, including patients with AIDS. Safety risks, together with the inconvenience of administering an intravenous drug for a prolonged period of time, led to the development of oral ganciclovir. Oral ganciclovir (currently not available in the United States) was approved for prophylaxis of CMV disease in solid organ transplant recipients and in individuals with advanced HIV infection who are at risk of developing CMV disease. Oral ganciclovir is also approved as an alternative to the intravenous formulation for maintenance treatment of CMV retinitis. However, this formulation has poor bioavailability and prophylaxis requires that the patients take four capsules three times daily, making compliance challenging. The poor bioavailability of oral ganciclovir and the limitations of the

use of intravenous ganciclovir led to the development of valganciclovir, a more orally bioavailable prodrug form of ganciclovir. Valganciclovir is approved for CMV prophylaxis in solid organ transplant recipients and for the treatment of CMV retinitis in patients with AIDS. Foscarnet and cidofovir are approved for the treatment of CMV retinitis. They are also used off-label for the treatment of CMV infection in transplant recipients. As previously stated, because of their associated toxicities, their role in CMV infections in transplant patients has been limited to patients who are failing ganciclovir/valganciclovir, presumably due to drug resistance or to those who are intolerant to ganciclovir/valganciclovir due to neutropenia.

Letermovir is a first-in-class inhibitor of the cytomegalovirus (CMV) DNA terminase complex. In this submission, the Applicant seeks approval of letermovir for prophylaxis of CMV infection and disease in adult CMV seropositive recipients of an allogeneic HSCT, a field of an unmet medical need.

3. Product Quality

Two dosage forms of letermovir have been developed: tablets under NDA 209939 and injection under NDA 20940.

Tablet:

The drug products are immediate-release tablets with the following appearance:

- 240 mg: yellow, oval shaped tablet debossed with "591" on one side and the Merck logo on the other side.
- 480 mg: Pink, oval, bi-convex, tablet debossed with "595" on one side and the Merck logo on the other side.

The two strengths are proportional in terms of composition. In addition to the letermovir drug substance, the tablets include the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone 25, colloidal silicon dioxide, magnesium stearate, (b) (4) Carnauba Wax, and (b) (4). The (b) (4) film coating contains lactose monohydrate, hypromellose 2910, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (480 mg tablet only). The intended commercial product differs from the phase 3 formulation (b) (4) (b) (4) (b) (4).

The commercial packaging is in aluminum-aluminum blisters, with 7 tablets per blister card. In one configuration, a 1-month carton holds 4 child-resistant dose packages for a total of 28 tablets. In a second configuration, designed for in-patient use, a carton contains two 7-count blister cards for a total of 14 tablets. An expiration dating period of 30 months appears appropriate for both strengths when stored under USP controlled room temperature conditions.

Injection:

Letermovir injection for intravenous use is supplied as a sterile clear solution of 240 mg (12 mL per vial) or 480 mg (24 mL per vial). It is administered as an intravenous infusion at a constant rate over one hour after dilution. The final solutions for injection are obtained by

dilution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. The major excipient is the drug product hydroxypropyl β-cyclodextrin which is used as a drug solubilizer. The 240 mg and 480 mg letermovir doses contain 1800 mg and 3600 mg of hydroxypropyl β-cyclodextrin, respectively.

The single dose vials are supplied in cartons that contain 240 mg single-dose vial or 480 mg single-dose vial. Based on the provided stability data, an expiration dating period of 30 months appears appropriate for both strengths when stored under USP controlled room temperature conditions.

The use of hydroxypropyl β-cyclodextrin as (b) (4) has been associated with nephrotoxicity in animal studies and has been shown to accumulate in humans with renal impairment. However, the amount of hydroxypropyl β-cyclodextrin contained in both letermovir doses is less than the maximum daily parenteral dose recommended by the European Medicines Agency (160 mg/kg/day for persons older than 2 years of age). Further, 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.

At the time of writing this Cross Discipline Team Leader review, the Office of Compliance has not confirmed an Overall Acceptable recommendation. At the present time, inspection of (b) (4) is on-going. This is a follow-up to the inspection of (b) (4) This facility manufactures (b) (4)

Additionally, evaluation of results from preapproval inspections of the following facility is on-going at this time:

- (b) (4)

Three other facilities have been determined to be acceptable based on file review.

Please see the Office of Product Quality reviews for letermovir tablets and injection for additional details.

4. Nonclinical Pharmacology/Toxicology

The safety profile of letermovir has been evaluated extensively in nonclinical studies including in vitro studies and studies in mice, rats, monkeys, and dogs. Dr. David McMillan recommended approval of this NDA based on his review of the nonclinical safety information provided in this submission. Please refer to the Pharmacology/Toxicology review by Dr. David McMillan for additional details.

All safety pharmacology studies (cardiovascular, respiratory, neurological, renal, and gastrointestinal) and genotoxicity studies were negative. Letermovir was not associated with phototoxicity or skin irritation. However, slight local intolerance occurred when letermovir

was administered intravenously, intra-arterially, and intramuscularly. Carcinogenicity studies were not conducted given the relatively short duration of treatment (100 days) for the proposed indication (less than 6 months).

Of some concern in the preclinical toxicology studies was the finding of testicular toxicity observed in rats in the 4-week and 13-week repeat-dose toxicity studies and the male fertility studies at a letermovir dose of 180 mg/kg/day. The male reproductive toxicity findings were characterized by decreased testis and epididymis weights, minimal to massive degeneration of the spermatogenic epithelium in the testes, and minimal to marked oligospermia in the epididymis in male rats. Partial recovery of these effects was noted after a 4-week treatment free period following the 13-week repeat-dose toxicity study. However, testicular toxicity findings were irreversible in the male rat fertility study at exposure ≥ 3 times higher than the human exposure at the recommended human dose (RHD). No testicular effects were observed at doses resulting in letermovir exposures less than the human exposure at the RHD. Interestingly, testicular toxicity findings were not observed in the repeat-dose chronic toxicity study (26 weeks) in rats with doses similar to those used in the 13-week study. In addition, no male reproductive system effects were observed in a 13-week repeat-dose study in mice or in a 13-week testicular toxicity study in male monkeys up to the highest doses tested. The absence of testicular toxicity in species other than the rat, and the lack of testicular toxicity in the 26-week repeat-dose toxicity study in rats at doses that produced exposures approximately 11-fold higher than those observed in humans at the RHD, indicate that testicular toxicity appears to be limited to rats at high doses and that the testicular toxicity risk for humans appears to be low.

In addition to male reproductive system toxicities, hepatic/hepatobiliary systems and kidney were identified as sites of treatment-related toxicities. Adverse liver effects included minimal to moderate centrilobular fat deposition and hypertrophy, elevated bilirubin and alkaline phosphatase in the rat 4-week and 13-week repeat-dose toxicity studies (at doses 180 mg/kg/day, approximately 6 times higher than the exposure observed in humans at the RHD), but not in the 26-week study.

Adverse kidney effects attributed to the vehicle, hydroxypropyl β-cyclodextrin, consisting of decreased kidney weight and minimal to moderate tubular vacuolation, were also observed in all animals including controls in the IV rat studies.

In the embryofetal development studies, toxicity including fetal malformations was observed in rats at letermovir exposures 11 times higher than the human exposure at the RHD (based on the intravenous administration). In the pre/postnatal development study in rats, total litter loss and slight developmental delays in vaginal opening and pinna unfolding were observed at maternal letermovir exposures approximately 2 times higher than human exposure at the RHD.

In summary, animal studies identified liver and to a lesser extent the male reproductive system as potential target organs to be monitored and reviewed in clinical trials. Kidney was also identified as a potential target in patients receiving the intravenous formulation.

5. Clinical Pharmacology

Approval is recommended from the Office of Clinical Pharmacology Review (Mario Sampson, PharmD, Jeffrey Florian, PhD, Christian Grimstein, PhD, Jielin Sun, PhD, and Islam Yiounis, Ph.D). This section provides a brief summary of key clinical pharmacology findings for letermovir. Please refer to the clinical pharmacology review for additional details.

General clinical pharmacology considerations:

The pharmacokinetics of letermovir have been characterized following oral and intravenous administration in healthy subjects and HSCT recipients.

Absorption: After oral administration, letermovir is absorbed rapidly with a median time to maximum plasma concentrations (T_{max}) of 0.75 to 2.25 hours.

Distribution: Protein binding is about 99% in vitro. Hepatic uptake is mediated by OATP1B1/3.

Food effect: In a food effect study (high fat and calorie meal versus fasted) letermovir exposure was not significantly changed.

Bioavailability: In a population pharmacokinetic analysis, the absolute bioavailability in healthy adults and patients was estimated at 94% and 35%, respectively.

Pathway of elimination, including metabolism, half-life, and excretion:

Metabolism is a minor elimination pathway for letermovir. Letermovir is primarily eliminated in feces as an unchanged parent drug. Urinary excretion is less than 2% of the dose. The mean terminal half-life of letermovir is approximately 12 hours after a 480 mg intravenous dose in in healthy adults. Steady-state levels are reached within 9-10 days.

Intrinsic factors potentially affecting elimination:

Age, gender, and race: Neither age nor gender was found to be a significant covariate for drug exposure. With regards to race, an early pharmacokinetic study showed 1.5- to 2.5-fold increase in letermovir exposures among Japanese female subjects. It was initially hypothesized that genetic polymorphisms in OATP1B1 may be responsible for the higher exposures observed in Japanese female subjects (systemic exposures are higher due to hepatic uptake and subsequent slower elimination). However, a pharmacokinetic study in healthy Americans of Japanese ancestry concluded that the rs4149056 genotype did not contribute to the higher exposures observed in Japanese subjects and allowed for the inclusion of Asian people in the pivotal phase 3 study (P001). Results from a population pharmacokinetic substudy during the phase 3 trial demonstrated that among Japanese subjects letermovir exposures were less than 50% higher than letermovir exposures in non-Asian patients, findings considered not to be clinically significant.

It should be noted, however, that the pharmacokinetics of letermovir have not been studied in pediatric patients (< 18 years of age).

Hepatic impairment: The hepatic impairment study was conducted using substantially lower doses of letermovir than the recommended clinical dose: a 60 mg dose (once daily for 8 days) was used for the group with moderate hepatic impairment (Child-Pugh B) and 30 mg dose (once daily for 8 days) for the group with severe hepatic impairment (Child-Pugh C). The results of the pharmacokinetic study revealed that letermovir systemic exposures were higher in patients with hepatic impairment compared to those in healthy subjects. Subjects with moderate hepatic impairment had approximately 1.6-fold higher systemic exposures compared to healthy subjects. Systemic exposures in subjects with severe hepatic impairment were 3.8-fold higher than those in healthy volunteers. Because letermovir has a saturable elimination process (OATP-mediated hepatic update) and exposure changes observed prior to saturation (i.e, at a relatively lower dose) may represent the worst case scenario, it was decided that the data from the hepatic impairment study could be used to inform labeling. Physiologically based pharmacokinetic modelling (PBPK) simulations were consistent with this hypothesis. The clinical pharmacology review team agreed with the Applicant's proposal that no dose adjustment is necessary for patients with mild or moderate hepatic impairment, and use in patients with severe hepatic impairment is not recommended.

Renal impairment: The renal impairment study evaluated the pharmacokinetics of letermovir in subjects with moderate and severe renal impairment compared to healthy adults. This study was conducted using a 120 mg dose of letermovir (once daily for 8 days), a dose that is lower than the recommended clinical dose. The letermovir AUC exposure was 1.9 – and 1.4-fold higher in subjects with moderate and severe renal impairment compared to that in healthy subjects. Because letermovir has a saturable elimination process (OATP-mediated hepatic update) and exposure changes observed prior to saturation (i.e, at a relatively lower dose) may represent the worst case scenario, it was decided that the data from the renal impairment study could be used to inform labeling. The less than 2-fold increase in letermovir exposure in patients with moderate or severe renal impairment is not of concern considering that no exposure-safety relationships were not identified in the phase 3 trial. Based on these data, the Applicant's proposal that no dose adjustment is needed for patients with renal impairment was considered acceptable.

Drug-drug interactions

Many clinically relevant drug interactions were anticipated because letermovir is:

- inhibitor of CYP3A, CYP2C8, BCRP, BSEP, MRP2, OATP1B1/3, and OAT3
- inducer of CYP2B6 and CYP3A
- substrate of UGT1A1/3, CYP3A, CYP2D6, CYP2J2, OATP1B1/3, and P-gp

As a result of this anticipation, the Applicant conducted extensive drug-drug interaction studies with other drugs that are likely to be co-administered in the indicated population. Please refer to Tables 3, 5, and 6 in the product labeling for the results of these interaction studies and recommendations on how to manage interactions or how to avoid interactions. For detailed information about the drug-drug interactions, please also see the review by the

Clinical Pharmacology review team. Below is a brief description of drug-drug interaction studies with cyclosporine and voriconazole, drugs commonly used in transplant patients.

Interaction between letermovir and cyclosporine: Letermovir is an OATP1B1 substrate and cyclosporine is an OATP1B1 inhibitor. In a phase 1 drug-drug interaction study, cyclosporine increased the AUC of oral letermovir by 2-fold. As a result of this finding, the letermovir dose (oral or intravenous) was reduced from 480 mg to 240 mg when co-administered with cyclosporine in Trial P001. It is notable that almost half of the patients in the phase 3 trial used concomitant cyclosporine. Although the letermovir exposures in Trial P001 differed by route of administration and the use of cyclosporine (Table 2), the exposure-efficacy relationships were flat. Therefore, the proposed dosing regimen 480 mg orally or intravenously once daily (240 mg once daily when given with cyclosporine) was considered acceptable.

Table 1. Letermovir AUC values (ng*h/mL) in Trial P001

N	Letermovir dose (mg)	Letermovir route of administration	Use of cyclosporine	Median AUC (90% prediction interval)
139	480	PO	No	34,400 (16900, 73,700)
10	480	IV	No	100,000 (65,300, 148,000)
139	240	PO	Yes	60,800 (28,700, 122,000)
5	240	IV	Yes	70,300 (46,200, 106,000)

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

Interaction between letermovir and voriconazole: Voriconazole is a substrate of CYP2C9, CYP2C19, and CYP3A. In vitro, letermovir was found to induce CYP3A but did not induce CYP2C19. CYP2C9 was not evaluated. In a drug interaction study with voriconazole, the voriconazole AUC decreased by 44%. This was probably due to the induction of CYP2C9 by letermovir. The clinical implications of this drug interaction are clearly stated in the drug label. It is stated that if concomitant administration of voriconazole is necessary, close monitoring for reduced effectiveness of voriconazole is recommended. It is noteworthy that in Trial P001 investigators were made aware of this potential interaction between letermovir and voriconazole and use of voriconazole was not recommended unless it was deemed necessary. Ultimately, about 28% of the subjects in either arm (letermovir or placebo) received voriconazole during the treatment phase of the study. Interestingly, the number of subjects who experienced a serious on-treatment fungal infection was similar between the two arms (1.6% of the letermovir subjects versus 1% of the placebo subjects).

Formulation:

The pivotal clinical trial (Trial P001) was performed with the to-be-marketed oral and intravenous formulations; therefore, bridging studies between formulations are not required.

QT study or other QT assessment:

The Applicant conducted a thorough QT study in adult subjects and the results were reviewed by FDA's Interdisciplinary Review Team. In this double-blind, four-period, 8-sequence crossover study, 38 subjects received letermovir 480 mg IV (clinical dose), letermovir 960 mg (supratherapeutic dose), placebo, and moxifloxacin 480 mg.

No significant QTc prolongation effect of letermovir (letermovir 960 mg IV supra-therapeutic dose and 480 mg IV clinical dose) was detected in this thorough QT study. The largest upper bound of the 2-sided 90% CI for the mean differences between letermovir (single dose of 480 mg IV and 960 mg IV) and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcP for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated, indicating that assay sensitivity was established.

6. Clinical Microbiology

Please refer to the joint virology review by Dr. Takashi Komatsu and Dr. Anamaris Colberg Poley for detailed assessment of the non-clinical and clinical virology data. Overall the virology reviewers concluded that this NDA should be approved.

Briefly, letermovir is an inhibitor of the CMV terminase complex (pUL51/pUL56/pUL89) which is necessary for the generation of unit length DNA genomes from viral DNA concatemers for packing and subsequent virion maturation. 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 HCMV gB genotypes 1, 2, 3, and 4, respectively. Antagonism was not demonstrated when letermovir was combined with other anti-CMV drugs (ganciclovir, cidofovir, foscarnet, and acyclovir) indicating that in a cell culture model inhibition of CMV DNA polymerase does not antagonize concurrent inhibition of CMV DNA terminase. Selection in cell culture for CMV resistant to letermovir resulted in amino acid substitutions in pUL56 (L51M, V231A/L, V236L/M, E237D, L241P, T244K/R, L257I, F261C/L/S, Y321C, C325F/R/Y, M329T, and R369G/M/S). Most of these amino acid substitutions conferred decreased susceptibility to letermovir by several fold. CMV resistant mutants were still susceptible to ganciclovir, cidofovir and foscarnet as expected based on the different mechanism of action (CMV DNA polymerase inhibitors). No amino acid substitutions conferring resistance were detected in the other components of the terminase complex (pUL51 and pUL89).

Resistance in clinical studies: In the phase 3 pivotal clinical trial (P001) DNA sequence analysis of the entire coding regions of UL56 and UL59 was performed on samples from 28 letermovir-treated subjects who experienced prophylaxis failure and for whom samples were available for sequence analysis. Eight of the 28 subjects failed while on-treatment, whereas the remaining subjects failed after treatment discontinuation. Two of the 8 subjects with on-treatment failure were found to have a letermovir resistance substitution pUL56 V236M or C325W. The pUL56 V236M is a known resistance substitution identified in cell culture

selection for CMV resistance to letermovir and C325W is at a known resistance-associated position (C325F/R/Y has been selected in cell culture). Another subject who experienced on-treatment prophylaxis failure had a pUL56 E237G substitution at frequency less than 5% (the cut-off used by the Applicant for their analyses). While pUL56 E237D was associated with resistance in cell culture, the clinical significance of pUL56 E237G at this frequency is unknown. None of the 20 subjects who failed off-treatment was identified with resistance-associated amino acid substitutions. Of note, the pUL56 V236M resistance amino acid substitution was also identified from one subject with on-treatment failure from the supportive phase 2b trial.

The resistance data described above from the clinical trials as well as the resistance data from cell culture selection were agreed upon by the Applicant and will be reflected in the appropriate sections of the label.

7. Clinical/Statistical-Efficacy

This section summarizes the results of the efficacy analyses conducted by the review team for the key trial supporting the Applicant's proposed indication for the approval of letermovir for CMV prophylaxis in adult allogeneic CMV-seropositive HSCT recipients. This section will primarily focus on the phase 3 pivotal trial (P001). Please refer to the Clinical Review by Dr. Aimee Hodowanec, the Virology Review by Dr. Takashi Komatsu and Dr. Anamaris Colberg Poley, and the Statistical Review by Dr. Fraser Smith for complete details. Overall, the independent analyses by FDA reviewers confirmed the Applicant's primary and secondary efficacy findings for the pivotal trial.

Trial P001

Trial P001 was a phase 3, randomized, placebo-controlled, multi-center, double-blind trial of letermovir for the prevention of clinically significant CMV infection in adult CMV-seropositive allogeneic HSCT recipients. Eligible HSCT recipients were randomized in a 2:1 ratio to receive either letermovir or placebo. Study drugs were initiated at any time from the day of transplantation until 28 days post-transplantation. Each subject received assigned study drug through week 14 (~100 days) post-transplant. Both oral (tablet) and intravenous (IV) formulations of letermovir (and placebo) were available for study therapy. Subjects initiated treatment with the oral (tablet) formulation of study therapy provided they were able to swallow and did not have a condition (e.g., vomiting, diarrhea, or a malabsorptive condition) that might interfere with the absorption of the tablets. For subjects who couldn't swallow and/or had a condition that interfered with the absorption of the oral formulation, study therapy was initiated with or switched to the IV formulation. The IV formulation was switched to oral study therapy as soon as such subjects were able to swallow and/or the condition necessitating the use of the IV formulation resolved. After the end of study therapy, subjects were followed through Week 24 post-transplantation. Additionally, subjects had follow-up visits at Weeks 32, 40, and 48 post-transplantation.

The dose of letermovir was either 240 mg once daily for subjects receiving concomitant cyclosporine A (CsA), or 480 mg once daily, if the subject was not on CsA. Placebo for

letermovir was administered to maintain study blind. Enrolled subjects were stratified by study center and risk factor for reactivation of CMV disease.

The primary efficacy endpoint of the trial was the proportion of subjects with clinically significant CMV infection through Week 24 (~6 months) post-transplantation, 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.

Determination of CMV end-organ disease was based on the definition by Ljungman et al. (Clinical Infectious Diseases 2002;34:1094-1097) and confirmed by an independent, blinded Clinical Adjudication Committee. The viral load thresholds for initiation of preemptive treatment in this trial were based on risk factor for reactivation of CMV disease (see below risk categories) and were as follows:

During study treatment (through Week 14 post-transplantation):

- High risk: viral DNA ≥ 150 copies/mL
- Low risk: viral DNA> 300 copies/mL

After Week 14 post-transplantation:

- High risk: viral DNA ≥ 300 copies/mL
- Low risk: viral DNA> 300 copies/mL

Secondary efficacy endpoints:

- Proportion of subjects with clinically significant CMV infection through Week 14 (~100 days) post-transplant
- Time to onset of clinically significant CMV infection through Week 24 (~6 months) post-transplant.
- Proportion of subjects with CMV disease through Week 14 post-transplant and Week 24 post-transplant.
- Proportion of subjects with initiation of preemptive therapy for documented CMV viremia through Week 14 post-transplant and Week 24 post-transplant.
- The time to initiation of preemptive therapy for documented CMV viremia through Week 24 post-transplant.

Subject demographics:

Subject demographics are summarized in Table 2. As shown in the table, the demographic characteristics appeared to be well balanced between the treatment arms. The mean age was 51 years in both groups. Approximately 40% of the subjects were females and more than 80% were white. Approximately 50% of the subjects in both treatment arms were enrolled in Europe and approximately 40% in North America. A notable finding is the low representation of Blacks (2% in each arm) and Hispanics (8% in the letermovir arm and 5% in the placebo arm).

Table 2. Subject demographics (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)

The primary reason for transplantation was acute myeloid leukemia (approximately 38% in each arm) followed by myelodysplastic syndrome (17% in the letermovir arm and 12% in the placebo arm).

Efficacy results

Primary efficacy results: The primary efficacy results are displayed in Table 3. Clinically significant CMV infection was observed in 18% of subjects in the letermovir arm and 42% of subjects in the placebo arm

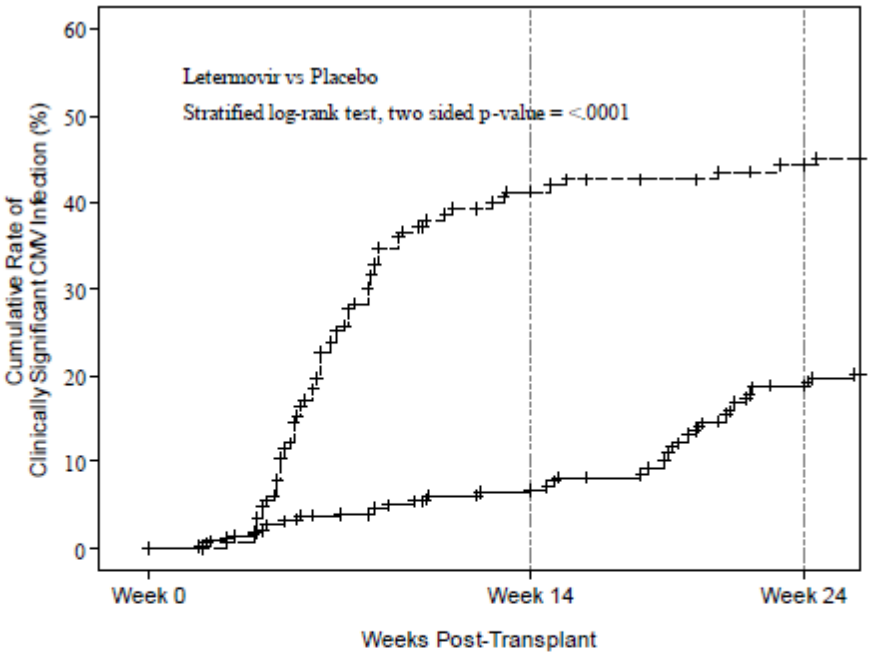
The majority of subjects who experienced clinically significant CMV infection had CMV viremia. CMV end-organ disease was very low in both arms (2% in each arm). This was not unexpected given the close CMV monitoring and initiation of preemptive therapy after detection of CMV DNAemia.

Table 3. Primary efficacy analysis: Clinically significant CMV infection through Week 24 post-transplantation

Efficacy parameter	**Letermovir N=325**	**Placebo N=170**	***P* value**
Overall failures	**122 (38%)**	**103 (61%)**	-23.5 (-32.5, -14.6), <0.001
Clinically significant CMV infection by Week 24	57 (18%)	71 (42%)	<0.001
Initiation of PET	52 (16%)	68 (40%)	
CMV end-organ disease	5 (2%)	3 (2%)	
Discontinued from study	57 (18%)	28 (16%)	
Missing outcome	8 (4%)	4 (2%)	

The Applicant also conducted a time to onset of clinically significant CMV infection which is shown in the following figure.

Figure: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 (full analysis 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)

The time to onset of clinically significant CMV infection through Week 24 was also significantly longer in the letermovir arm compared to placebo. However, it should be noted that the difference in magnitude decreased between Week 14 and Week 24. In fact, through Week 14 clinically significant CMV infection was observed in 8% of subjects in the letermovir group and in 39% of subjects in the placebo group. This finding may indicate that in some subjects CMV is suppressed during the treatment phase of the study, but rebounds after letermovir discontinuation.

Subgroup analyses of primary endpoint:
Additional analyses found that letermovir was favored in the primary efficacy analysis in each gender, median age, whites, non-Asian, and non-Hispanic ethnic groups, which were the subgroups with the most patients. In many of these subgroups the difference was statistically significant. An exception to this was the Asian race and Hispanic ethnicity (subgroups with fewer patients) where no difference between the letermovir and placebo arm was observed. The Black subgroup was too small to perform a meaningful analysis.

Mortality:

Mortality was an exploratory efficacy endpoint for this trial. Interestingly, the Kaplan-Meier event rate for all-cause mortality was lower for the letermovir arm (12%) compared to the placebo arm (17%) through Week 24; this difference was statistically significant (two-sided *p* value = 0.04). A trend favoring letermovir was also observed for all-cause mortality through Week 48 post-transplantation (24% in the letermovir arm versus 28% in the placebo arm). However, the difference in all-cause mortality through Week 48 was not statistically significant (two-sided *p* value = 0.21).

Whether the decreased all-cause mortality was impacted by letermovir or it was an accidental statistical observation is not clear. Tissue-invasive CMV disease was very low and similar in both arms (2% in each arm). The incidence of GVHD was also similar between the treatment arms. Further, no death in either arm appeared to be directly attributable to CMV infection. However, all-cause mortality findings are in line with recent publication suggesting that CMV viremia is associated with an increased risk of overall mortality in the first year after HSCT (Green ML et al. Lancet Haematol 2016:e119-127).

Trial P020

This was a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging trial to assess the safety, tolerability, and prophylactic anti-CMV activity of letermovir in adult CMV-seropositive subjects who underwent HSCT. Following transplantation and transplant engraftment, eligible subjects were randomized to receive letermovir or placebo in a 3:1 ratio to three sequential study cohorts (starting from the low dose). Patients received letermovir (60 mg qd, 120 mg qd, or 240 mg qd) or placebo administered orally once daily for 12 weeks.

The primary efficacy endpoint of the trial was CMV prophylaxis failure within the 12-week treatment period.

CMV prophylaxis failure was defined as:

- Two CMV blood samples tested positive in the local laboratory which was drawn at separate consecutive time-points (i.e., no negative samples at any intervening time-point) and which led to the discontinuation of the trial medication and to the initiation of treatment with an alternative CMV anti-viral medication.

  In addition, one CMV blood sample from either of the two time-points testing positive in the local laboratory must also have tested positive in the central laboratory.

. Or

- If the patient developed CMV end-organ disease as defined by Ljungman et al. (Clinical Infectious Diseases 2002;34:1094-1097).

Efficacy results:
The efficacy results are summarized in Table 4.

Table 4: P020 - Failure of prophylaxis within the 12-week treatment period.

Efficacy parameter	Placebo N=33	Letermovir dose group		
		60 mg QD N=33	120 mg QD N=31	240 mg QD N=34
Failed, n (%)				
Yes	21 (63.6)	16 (48.5)	10 (32.3)	10 (29.4)
CMV prophylaxis failed	12 (36.4)	7 (21.2)	6 (19.4)	2 (5.9)
Other discontinuation	9 (27.3)	9 (27.3)	4 (12.9)	8 (23.5)
No	12 (36.4)	17 (51.5)	21 (67.7)	24 (70.6)
Odds ratio for failure with letermovir vs. placebo (95% CI)		0.54 (0.18-1.60)	0.27 (0.08-0.86)	0.24 (0.08-0.74)
P value (all cause failure with letermovir vs. placebo)		0.32	0.01	0.07

The results showed fewer prophylaxis failures in each of the letermovir groups compared to placebo, with the rate of CMV prophylaxis failure decreasing with increasing the letermovir doses. The difference was statistically significant in the 120 mg/day and 240 mg/day groups when compared with placebo (32.3% [10/31], p=0.014 and 29.4% [10/34], p=0.007, respectively). None of the patients with detectable CMV replication had CMV end-organ disease.

8. Safety

The safety database for letermovir 480 mg once daily (240 mg when coadministered with cyclosporine) for approximately 100 days is adequate for the proposed indication. CMV is a serious and life-threatening disease in HSCT recipients and letermovir has received an orphan drug designation. The phase 3 pivotal trial (P001) was the primary basis for the safety analysis because lower letermovir doses than that proposed for approval were used in P020. For details of clinical safety, see the Clinical Review by Dr. Aimee Hodowanec.

Overall, the safety profile of letermovir was acceptable. In trial P001, nausea, diarrhea, pyrexia, and rash were the most commonly reported adverse events (> 20%) among letermovir subjects and occurred at a similar rate in patients in the placebo group. Similar rates in major laboratory abnormalities were also observed between the two treatment groups. In many cases, numerical differences in rates for adverse events or laboratory abnormalities between the letermovir arm and the placebo arm may have been due to the longer duration of study drug exposure in patients in the letermovir arm. The study design required discontinuation of study medication for clinically significant CMV infection. Given the significantly lower incidence of clinically significant CMV infection or disease in the letermovir arm compared to the placebo arm, the median duration of therapy was longer for subjects in the letermovir arm (82 days)

than for subjects receiving placebo (56 days). As treatment emergent events and laboratory abnormalities were defined as those occurring within 2 weeks of completion therapy, this translates into a 22% longer duration of adverse event and laboratory abnormality reporting in the letermovir arm compared to placebo. When exposure-adjusted analyses were performed, most of the differences in adverse events between the treatment arms disappeared. Cardiac adverse events were the major difference between subjects who received letermovir and placebo (12.6% versus 6.3%). The difference between the two arms was only slightly changed after exposure-adjusted analysis (13.6% versus 8.2%). The most common cardiac adverse events were tachycardia (in 4% of letermovir subjects and 2% of placebo subjects) and atrial fibrillation (in 4% of letermovir subjects and in 1% of placebo subjects). Most of these events were mild or moderate in severity, they were confounded by pre-existing medical conditions and the use of other medications, and they were considered by the investigators as not related to study drugs. Of note, more patients in the letermovir arm had a baseline cardiac medical history (30% in the letermovir arm versus 25% in the placebo arm) and none of the cardiac adverse events was assessed by the investigators as drug related.

The Division of Cardiovascular and Renal Products (DCRP) was consulted to assist with interpretation of the cardiac adverse events and to provide recommendations regarding appropriate labeling and potential future studies. They recommended including a general description of the cardiac events in the product label. No additional studies were recommended by DCRP. The Division of Applied Regulatory Science/Office of Clinical Pharmacology was also consulted (DARS/OCP) by the Division to utilize computational models to identify potential structural components that may be associated with this cardiac signal. All of the hypotheses suggested by DARS/OCP were addressed by the Applicant who found no association. The Applicant concluded that no further investigation of the potential targets identified by the FDA was warranted. DARS/OCP agreed with the Applicant's conclusions.

The percentage of subjects with serious adverse events, drug-related adverse events, discontinuations due to a drug-related adverse event, or due to a serious drug-related adverse event was similar between the two treatment arms.

Of concern was also the use of hydroxypropyl β-cyclodextrin (b) (4) in the intravenous formulation because it has been associated with nephrotoxicity in animal studies and has been shown to accumulate in humans with renal impairment. As stated in Section 3, the amount of hydroxypropyl β-cyclodextrin contained in both letermovir doses is less than the maximum daily parenteral dose recommended by the European Medicines Agency (160 mg/kg/day for persons older than 2 years of age). Further, the safety profile of the patients who received intravenous letermovir was similar to those who received placebo. The only significant difference was the incidence of hyperglycemia which was probably secondary to the 5% dextrose that could be used to dilute the intravenous formulation (hyperglycemia was observed in 7% of patients who received intravenous formulation and in 4% in those who received placebo).

Adverse events of clinical significance identified during the letermovir development program:

Testicular toxicity: As previously stated in Section 4, letermovir caused testicular toxicity in rats (at high doses) but not in other animal species. To further evaluate the potential of testicular toxicity in humans, serum inhibin B (a surrogate endpoint of testicular function), LH, FSH, and testosterone levels were measured at baseline, at the end of treatment, and at Week 24 post-transplantation in Trial P001. No semen analysis was performed. To help interpret the results and to determine whether a postmarketing study was needed in which semen parameters would be evaluated, the Division of Bone, Reproductive and Urology Products (DBRUP) was consulted. They concluded that the provided data showed no clinically relevant effect of letermovir on male sex hormones. However, male sex hormones should not be considered as adequate biomarkers for potential injury to seminiferous tubules and germ cells. Based on the reasons explained in Section 4, they concluded that testicular toxicity appears to be limited in rat species and that the testicular toxicity risk for humans is very low. After a thorough discussion with interdisciplinary team participation, it was decided that a PMR for testicular toxicity is not needed.

Hepatic/hepatobiliary toxicity: Hepatic/hepatobiliary were identified as potential treatment-related toxicities based on preclinical toxicology studies. The percentage of subjects with hepatobiliary disorders was similar between the two treatment arms (6% in the letermovir arm versus 8% in the placebo arm). There were 11 subjects in Trial P001 who met the Hy's Law criteria; 8 subjects (2.1%) were in the letermovir arm and 3 (1.6%) in the placebo arm. As stated in Dr. Aimee Hodowanec's review none of the cases is likely to represent DILI.

Drug-related IV infusion-site adverse events: Early in development of the letermovir intravenous formulation (b) (4) formulation was used. That formulation was associated with mild to moderate injection site reactions. Because of these reactions, the intravenous formulation was changed to a hydroxypropyl betadex formulation. In trial P001, two of the 99 subjects (2%) who received letermovir intravenous formulation had infusion site reactions (one subject each with mild erythema and mild inflammation). None of the 48 subjects who received intravenous placebo had any infusion site reaction.

9. Advisory Committee Meeting

No Advisory Committee was held to discuss this application because this drug was granted a Breakthrough Therapy Designation and the benefit/risk assessment did not appear controversial based on the review team's preliminary assessment.

10. Pediatrics

Pediatric studies have not been initiated at this time. Of note, letermovir received an orphan drug designation on December 12, 2011, and is therefore exempt from Pediatric Research Equity Act (PREA) requirements. The Applicant was asked before the pre-NDA meeting to provide their plans to study letermovir in pediatric patients and to clarify whether they are interested in receiving a Pediatric Written Request (PWR). During the pre-NDA meeting (December 14, 2016) the (b) (4)

(b) (4)

Because letermovir has received an orphan drug designation and, therefore, does not trigger PREA, (b) (4)

A Proposed Pediatric Study Request has not been submitted by the Applicant to date.

11. Other Relevant Regulatory Issues

Financial disclosures

Financial disclosures were provided for the phase 2b trial (P020) and the pivotal phase 3 trial (P001). In trial P020 there were 114 investigators and none of them had a disclosable financial interest. In trial P001 there were 507 investigators and only one of them had a disclosable financial interest (spouse was a Merck employee). Due to the multicenter nature of the trial and trial design (randomized, double-blind) the potential for bias in the trial is negligible.

Other Good Clinical Practice (GCP) issues

The clinical trials were conducted in accordance with ICH Good Clinical Practice (GCP) Guidelines.

Office of Scientific Investigations (OSI) audits

At the request of the Division of Antiviral Products, the Office of Scientific Investigations (OSI) audited 5 sites from the pivotal phase 3 trial; 2 sites in the United States and 3 international sites. These sites were selected based on enrollment, protocol violations, and previous inspection history. Based on the inspections of the five clinical sites, the study appears to have been conducted adequately and the inspectional findings support the validity and acceptability of the data as reported by the Applicant under the two NDAs. Please refer to the OSI Consult Review for additional details

Other outstanding regulatory issues

The only unresolved regulatory issue at the time of writing this memorandum is final recommendations from the Office of Compliance regarding inspections of manufacturing facilities as discussed in Section 3 above.

12. Labeling

Prescribing Information

Letermovir prescribing information is currently in the final stages of negotiation with the Applicant. The Division has been working closely with the Applicant to ensure that the

product label is displayed in a clear, concise, transparent, and clinically meaningful as possible given the complexity of some of the label sections. Particularly difficult issues in this label were the subsections of "Preparation and Administration of Intravenous Solution", "Compatible Drug Products Used for Intravenous Administration", and the Sections of "Drug Interactions".

Preparation and Administration of Intravenous Solution: The complexity of this subsection was due to the fact that intravenous letermovir is not compatible with all IV bags, infusion materials and fluids. This subsection has been agreed upon by the Applicant and reads as follows:

2.6 Preparation and Administration of Intravenous Solution

PREVYMIS injection is supplied in 30 mL single-dose vials containing either 240 mg/12 mL per vial (20 mg/mL) or 480 mg/24 mL per vial (20 mg/mL). The preparation and administration instructions are the same for either dose.

PREVYMIS vials are for single use only. Discard any unused portion.

Preparation and Administration Instructions

- PREVYMIS must be diluted prior to intravenous (IV) use.

- Inspect vial contents for discoloration and particulate matter prior to dilution. PREVYMIS injection is a clear colorless solution. Do not use the vial if the solution is discolored or contains visible particles.

- Do not shake PREVYMIS vial.

- Add one single-dose vial of PREVYMIS injection into a 250 mL pre-filled IV bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix bag gently. Do not shake. Only 0.9% Sodium Chloride and 5% Dextrose are chemically and physically compatible with PREVYMIS injection.

- Use compatible IV bags and infusion set materials. PREVYMIS injection is compatible with the following IV bags and infusion set materials. PREVYMIS injection is not recommended with any IV bags or infusion set materials not listed below (note that PREVYMIS injection is not recommended to be used with polyurethane-containing IV administration set tubing).

  IV Bags Materials: Polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and polyolefin (polypropylene and polyethylene)

  Infusion Sets Materials:
  PVC, polyethylene (PE), polybutadiene (PBD), silicone rubber (SR), styrene–butadiene copolymer (SBC), styrene-butadiene-styrene copolymer (SBS), polystyrene (PS)

Plasticizers:
Diethylhexyl-phthalate (DEHP), tris (2-ethylhexyl) trimellitate (TOTM), benzyl butyl phthalate (BBP)

Catheters:
Radiopaque polyurethane

- Once diluted, the solution of PREVYMIS is clear, and ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.

- The diluted solution is stable for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2°C to 8°C (36°F to 46°F) (this time includes storage of the diluted solution in the intravenous bag through the duration of infusion).

- Administer the entire contents of the intravenous bag by intravenous infusion via a peripheral catheter or central venous line at a constant rate over 1 hour *[see Dosage and Administration (2.1)]*.

Compatible Drug Products Used for Intravenous Administration: The complexity of this subsection is similar to the previous subsection. This subsection has been discussed and agreed upon by the Applicant. The final version of this subsection reads as follows:

2.7 Compatible Drug Products Used for Intravenous Administration

Compatible Drug Products
The physical compatibility of PREVYMIS injection with selected injectable drug products was evaluated in two commonly available diluents. PREVYMIS should not be co-administered through the same intravenous line (or cannula) with other drug products and diluent combinations except those listed below. Refer to the respective prescribing information of the co-administered drug(s) to confirm compatibility of simultaneous co-administration.

List of Compatible Drug Products when PREVYMIS and Drug Products are Prepared in 0.9% Sodium Chloride Injection, USP:
Ampicillin sodium, ampicillin sodium/sulbactam sodium, anti-thymocyte globulin, caspofungin, daptomycin, fentanyl citrate, fluconazole, furosemide, human insulin, magnesium sulfate, methotrexate, micafungin.

List of Compatible Drug Products when PREVYMIS and Drug Products are Prepared in 5% Dextrose Injection, USP:
Amphotericin B (lipid complex)*, anidulafungin, cefazolin sodium, ceftaroline, ceftriaxone sodium, doripenem, famotidine, folic acid, ganciclovir sodium, hydrocortisone sodium succinate, morphine sulfate, norepinephrine bitartrate, pantoprazole sodium, potassium chloride, potassium phosphate, , tacrolimus, telavancin, tigecycline.

*Amphotericin B (lipid complex) is compatible with PREVYMIS. However, Amphotericin B (liposomal) is incompatible *[see Dosage and Administration (2.8)]*.

Drug Interactions: Given the numerous drug interactions of letermovir, the Division and the Applicant are still discussing how to present this section and provide appropriate recommendations on how to avoid or how to manage interactions.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Based on the overall safety profile of letermovir, a REMS is not recommended.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following is the Division's listing of recommended PMR/PMCs to date:

1. To further characterize resistance CMV resistance to letermovir the Division recommended the following post-marketing study. As resistance is considered a safety issue, the recommendation will be a PMR under FDAAA.

   Please conduct phenotypic analysis of letermovir against HCMV mutants carrying the following pUL56 and pUL89 substitutions using bacterial artificial chromosome technology:
   - High priority: pUL56 L134V, E237G, C325W, R410G, D414N, G430V, E485G, and E485G+445-SNS-447 deletion; pUL89 Q256E, L522P and Q625* (stop).
   - Low priority: pUL56 M3I/V, E157G, S255L, I313V, Y575C, L658S, S705F, R816W, R826L, and P846L; pUL89 N74S, P176S, D309G, M406V, I531V/T, and A532T.

   Please include previously identified substitutions with a range of susceptibilities from low fold change (e.g., pUL56 L257I) to high fold change (e.g., pUL56 C325Y) as references.

2. To further characterize potential drug interactions the Division recommended the following study:

   - Conduct an in vitro study to determine if letermovir is an inducer of cytochrome P450 enzymes CYP2C8, CYP2C9, or CYP2C19.

3. In order to investigate whether letermovir could also be used for CMV prophylaxis in high risk kidney transplant recipients, the Applicant submitted a draft protocol which was reviewed by the Division. The recommendation will be a PMC under FDAAA.

   - Submit the final study report and datasets from the proposed clinical trial, P002, entitled, "A phase III, randomized, double-blind, active comparator-controlled study to evaluate the efficacy and safety of letermovir versus valganciclovir for the prevention of human cytomegalovirus disease in adult kidney transplant recipients".

Draft Protocol Submission:	05/2017
Final Protocol Submission:	01/2018
Study/Trial Completion:	06/2022
Final Report Submission:	01/2023

4. During the Late Cycle Meeting (September 8, 2017) the Division proposed the following Post Marketing Commitment:

   CMV treatment trial to assess the efficacy and safety of letermovir for:
   - CMV infection in the blood and/or CMV end-organ disease in HSCT and/or in SOT recipients; and/or
   - CMV resistant/refractory infection in the blood and/or end-organ disease in HSCT and/or SOT recipients

   The Applicant's initial response was that they do not plan to do any clinical studies other than the prophylaxis trial in adult kidney transplant recipients that is described above. At the Division's request to consider conducting a small treatment trial, perhaps in combination with ganciclovir, the Applicant stated that they will discuss internally and inform the Division of their decision. On October 10, 2017, the Applicant informed the Division that they agree to conduct a small treatment trial; however, they do not agree that the conduct of this treatment trial be considered a post-marketing commitment.

5. The Division is considering for a PMR study to assess whether a longer duration of prophylaxis (200 days versus 100 days) reduces the rate of rebound CMV infection within a prespecified time-period post-transplantation following the discontinuation of letermovir prophylaxis. This issue will be presented to the Medical Council and Program Review Meeting for discussion and input.

14. Recommended Comments to the Applicant

There are no additional comments to be conveyed to the Applicant at this time.

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

/s/

ANDREAS PIKIS
10/11/2017