PREVYMIS™ Film Coated Tablet 240 mg
PREVYMIS™ Film Coated Tablet 480 mg
PREVYMIS™ Concentrate for Solution for Infusion 20 mg/mL

1. INDICATIONS AND USAGE

PREVYMIS is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

2. DOSAGE AND ADMINISTRATION

2.1 General

PREVYMIS Tablets

- Administer with or without food.
- Swallow tablets whole. Do not divide, crush or chew.

PREVYMIS Concentrate for Solution for Infusion

- PREVYMIS injection must be administered through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter.
- Administer by intravenous infusion via a peripheral catheter or central venous line over approximately 60 minutes.
- Do not administer as an intravenous bolus injection.

PREVYMIS tablet and concentrate for solution for infusion may be used interchangeably at the discretion of the physician, and no dose adjustment is necessary.

Missed Dose

Instruct patients that if they miss a dose of PREVYMIS, they should take it as soon as they remember. If they do not remember until it is time for the next dose, instruct them to skip the missed dose and go back to the regular schedule. Instruct patients not to double their next dose or take more than the prescribed dose.

2.2 Recommended Dosage in Adults

The recommended dosage of PREVYMIS is 480 mg administered once daily.

PREVYMIS should be started after HSCT. PREVYMIS may be started on the day of transplant and no later than 28 days post-transplant. PREVYMIS may be started before or after engraftment. Continue PREVYMIS through 100 days post-transplant.

The safety and efficacy of letermovir use for more than 100 days has not been studied in clinical trials.

2.3 Dosage Adjustment in Adults

If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily *[see Table 1 in 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Established and Other Potential Drug Interactions].*

- If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be decreased to 240 mg once daily.
- If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be increased to 480 mg once daily.

- If cyclosporine dosing is temporarily interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed.

2.4 Pediatric Patients

Safety and efficacy of PREVYMIS have not been established in pediatric patients less than 18 years of age.

2.5 Geriatric Patients

No dose adjustment of PREVYMIS is required based on age *[see 6 USE IN SPECIFIC POPULATIONS, 6.5 Geriatric Use]*.

2.6 Renal Impairment

No dose adjustment of PREVYMIS is required based on renal impairment *[see 2 DOSAGE AND ADMINISTRATION, 2.7 Hepatic Impairment, and 6 USE IN SPECIFIC POPULATIONS, 6.6 Renal Impairment].*

2.7 Hepatic Impairment

No dose adjustment of PREVYMIS is required based on mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

PREVYMIS is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment *[see 6 USE IN SPECIFIC POPULATIONS, 6.7 Hepatic Impairment].*

2.8 Preparation and Administration of Intravenous Solution

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

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

Preparation

- PREVYMIS must be diluted prior to intravenous (IV) use.
- Inspect vial contents for discoloration and particulate matter prior to dilution. PREVYMIS concentrate for solution for infusion is a clear, colorless solution and may contain a few product-related small translucent or white particles.
- Do not use the vial if the solution is cloudy, discolored, or contains matter other than a few small translucent or white particles.
- Do not use PREVYMIS injection with IV bags and infusion set materials containing polyurethane or the plasticizer diethylhexyl phthalate (DEHP). Materials that are phthalate-free are also DEHP-free.
- Do not shake PREVYMIS vial.
- Add one single-dose vial of PREVYMIS concentrate for solution for infusion to a 250 mL pre-filled IV bag containing either 0.9% sodium chloride or 5% dextrose and mix bag gently. Do not shake.
- 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. The diluted solution should be inspected visually for particulate matter and discoloration prior to administration.

- Discard if the diluted solution is cloudy, discolored, or contains matter other than a few small translucent or white particles.

Storage of Diluted Solution

- The diluted solution can be stored 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.

Administration

- The diluted solution must be administered through a sterile 0.2 micron or 0.22 micron PES in-line filter.

- Do not administer the diluted solution through a filter other than a sterile 0.2 micron or 0.22 micron PES in-line filter.

- Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus.

- After dilution, administer PREVYMIS via intravenous infusion via peripheral or central venous catheter using a total time of approximately 60 minutes. Administer the entire contents of the IV bag.

2.9 Compatible Diluents, Drug Products, and Other Materials Used for Intravenous Administration

Compatible Diluents

PREVYMIS concentrate for solution for infusion is compatible with 0.9% sodium chloride and 5% dextrose solutions.

Compatible Drug Products

A study was conducted to evaluate physical compatibility of PREVYMIS concentrate for solution for infusion with injectable drug products. Compatibility was determined through visual observations, turbidity, and measurement of particulate matter. Compatible drug products are listed below.

PREVYMIS should not be co-administered through the same intravenous line (or cannula) with other drug products and diluent combinations except those listed below.

The following compatible drug products may be co-administered with PREVYMIS for injection when both drug products are in 0.9% Sodium Chloride via Y tubing only, as per the approved instructions of the respective drug products.

- Ampicillin sodium
- Ampicillin sodium/Sulbactam sodium
- Anti-thymocyte globulin
- Caspofungin
- Daptomycin
- Fentanyl citrate
- Fluconazole
- Furosemide
- Human insulin
- Magnesium sulfate
- Methotrexate
- Micafungin

The following compatible drug products may be co-administered with PREVYMIS for injection when both drug products are in 5% Dextrose via Y tubing only, as per the approved instructions of the respective drug products.

- 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 2 DOSAGE AND ADMINISTRATION, 2.10 Incompatible Diluents, Drug Products, and Other Materials Used for Intravenous Administration]*.

Compatible IV Bags and Infusion Set Materials

PREVYMIS is compatible with the following IV bags and infusion set materials. Any IV bags or infusion set materials not listed below should not be used.

IV Bag Materials

Polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and polyolefin (polypropylene and polyethylene)

Infusion Set Materials

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

Plasticizers

Tris (2-Ethylhexyl) trimellitate (TOTM), butyl benzyl phthalate (BBP)

Catheters

Radiopaque polyurethane

2.10 Incompatible Diluents, Drug Products, and Other Materials Used for Intravenous Administration

Incompatible Drug Products

PREVYMIS concentrate for solution for infusion is physically incompatible with amiodarone hydrochloride, amphotericin B (liposomal), aztreonam, cefepime hydrochloride, ciprofloxacin, cyclosporine, diltiazem hydrochloride, filgrastim, gentamicin sulfate, levofloxacin, linezolid, lorazepam, midazolam HCl, mycophenolate mofetil hydrochloride, ondansetron, palonosetron.

Incompatible IV Bags and Infusion Set Materials

PREVYMIS concentrate for solution for infusion is incompatible with diethylhexyl phthalate (DEHP) plasticizers and polyurethane-containing IV administration set tubing.

3. CONTRAINDICATIONS

PREVYMIS is contraindicated in patients with hypersensitivity to letermovir or any of its inactive ingredients.

Pimozide
Concomitant administration of PREVYMIS may result in increased concentrations of pimozide due to inhibition of cytochrome P450 (CYP3A) by letermovir, leading to QT prolongation and torsades de pointes *[see 4 WARNINGS AND PRECAUTIONS, 4.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions, and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 Effects of PREVYMIS on Other Drugs].*

Ergot alkaloids
Concomitant administration of PREVYMIS may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism *[see 4 WARNINGS AND PRECAUTIONS, 4.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions, and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 Effects of PREVYMIS on Other Drugs]*.

Cyclosporine with pitavastatin or simvastatin
Concomitant administration of PREVYMIS in combination with cyclosporine may result in significantly increased pitavastatin or simvastatin concentrations, which may lead to myopathy or rhabdomyolysis *[see 4 WARNINGS AND PRECAUTIONS, 4.1, Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions, and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 Effects of PREVYMIS on Other Drugs].*

4. WARNINGS AND PRECAUTIONS

4.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of PREVYMIS and certain drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Possible clinically significant adverse reactions from greater exposure of concomitant drugs or PREVYMIS.
- Significant decrease of concomitant drug plasma concentrations which may lead to reduced therapeutic effect of the concomitant drug.

See Table 1 for steps to prevent or manage these known or potentially significant drug interactions, including dosing recommendations *[see 3 CONTRAINDICATIONS and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 Effects of PREVYMIS on Other Drugs, and 5.3 Established and Other Potential Drug Interactions].*

PREVYMIS should be used with caution with drugs that are CYP3A substrates with narrow therapeutic ranges (e.g., alfentanil, fentanyl, and quinidine) as co-administration may result in increases in the plasma concentrations of CYP3A substrates. Close monitoring and/or dose adjustment of co-administered CYP3A substrates is recommended. *[See Table 1 and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 Effects of PREVYMIS on Other Drugs, and 5.3 Established and Other Potential Drug Interactions]*.

The safety and efficacy of letermovir has been established in patients with a negative CMV DNA test result prior to initiation of prophylaxis. CMV DNA was monitored on a weekly basis until post-transplant Week 14, and subsequently bi-weekly until Week 24. In cases of clinically significant CMV DNAemia or disease, letermovir prophylaxis was stopped and standard-of-care pre-emptive therapy (PET) or treatment was initiated. In patients in whom letermovir prophylaxis was initiated and the baseline CMV DNA test was subsequently found to be positive, prophylaxis could be continued if PET criteria has not been met.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

5.1 Effects of Other Drugs on PREVYMIS

Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) and P-glycoprotein (P-gp) transporters and UDP-glucuronosyltransferase 1A1/3 (UGT1A1/3) enzymes. Co-administration of PREVYMIS with drugs that are inhibitors of OATP1B1/3 transporters may result in increases in letermovir plasma concentrations. If PREVYMIS is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor), the recommended dose of PREVYMIS is 240 mg once daily *[see 2 DOSAGE AND ADMINISTRATION, 2.3 Dosage Adjustment in Adults]*.

Co-administration of PREVYMIS with strong and moderate inducers of transporters (e.g., P-gp) and/or enzymes (e.g., UGTs) is not recommended due to the potential for a decrease in letermovir plasma concentrations (see Table 1).

Rifampin co-administration resulted in an initial increase in letermovir plasma concentrations (due to OATP1B1/3 inhibition) that is not clinically relevant, followed by clinically relevant decreases in letermovir plasma concentrations with continued rifampin co-administration *[see Table 5 in 10 CLINICAL PHARMACOLOGY, 10.5 Drug Interaction Studies]*.

5.2 Effects of PREVYMIS on Other Drugs

Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentrations, indicating that letermovir is a moderate inhibitor of CYP3A. Co-administration of PREVYMIS with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates *[see 3 CONTRAINDICATIONS, and 4 WARNINGS AND PRECAUTIONS, 4.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions]* and Table 1.

Letermovir is an inhibitor of OATP1B1/3 transporters. Co-administration of PREVYMIS with drugs that are substrates of OATP1B1/3 transporters may result in a clinically relevant increase in plasma concentrations of co-administered OATP1B1/3 substrates (see Table 1).

5.3 Established and Other Potential Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with PREVYMIS, doses should be readjusted after treatment with PREVYMIS is completed.

When PREVYMIS is co-administered with cyclosporine, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the prescribing information for dosing of the CYP3A substrate with a strong CYP3A inhibitor.

When PREVYMIS is co-administered with cyclosporine, the combined effect on agents that are both CYP3A and OATP1B1/3 substrates may be different than when they are administered with PREVYMIS alone. Refer to the prescribing information for both the co-administered drug and for cyclosporine.

Table 1 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with PREVYMIS or are predicted drug interactions that may occur with PREVYMIS *[see 4 WARNINGS AND PRECAUTIONS, 4.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions]*.

Table 1: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions*

Concomitant Drug Class and/or Clearance Pathway: Drug Name	**Effect on Concentration†**	**Clinical Comment**
Anti-arrhythmic Agents		
amiodarone	↑ amiodarone	Co-administration of PREVYMIS with amiodarone increases plasma concentrations of amiodarone. Close clinical monitoring for adverse events related to amiodarone is recommended during co-administration. Frequently monitor amiodarone concentrations.
Antibiotics		
nafcillin	↓ letermovir	Co-administration of PREVYMIS with nafcillin may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and nafcillin is not recommended.
Anticoagulants		
warfarin	↓ concentrations of warfarin	Co-administration of PREVYMIS with warfarin may decrease the plasma concentrations of warfarin. Frequent monitoring of INR should be performed while warfarin is co-administered with PREVYMIS§.
Anticonvulsants		
carbamazepine	↓ letermovir	Co-administration of PREVYMIS with carbamazepine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and carbamazepine is not recommended.
phenobarbital	↓ letermovir	Co-administration of PREVYMIS with phenobarbital may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and phenobarbital is not recommended.

phenytoin	↓ letermovir ↓ phenytoin	Co-administration of PREVYMIS with phenytoin may decrease plasma concentrations of letermovir. PREVYMIS may decrease the plasma concentrations of phenytoin. Co-administration of PREVYMIS and phenytoin is not recommended.
Antidiabetic Agents		
glyburide	↑ glyburide	Co-administration of PREVYMIS with glyburide may increase the plasma concentration of glyburide. Frequent monitoring of glucose concentrations is recommended§.
Antifungals		
voriconazole‡	↓ voriconazole	Co-administration of PREVYMIS with voriconazole decreases plasma concentrations of voriconazole. If concomitant administration is necessary, close monitoring for reduced effectiveness of voriconazole is recommended§.
Antimycobacterials		
rifabutin	↓ letermovir	Co-administration of PREVYMIS with rifabutin may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and rifabutin is not recommended.
rifampin‡	↓ letermovir	Co-administration of PREVYMIS with rifampin decreases plasma concentrations of letermovir. Co-administration of PREVYMIS and rifampin is not recommended.
Antipsychotics		
thioridazine	↓ letermovir	Co-administration of PREVYMIS with thioridazine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and thioridazine is not recommended.
Endothelin Antagonists		
bosentan	↓ letermovir	Co-administration of PREVYMIS with bosentan may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and bosentan is not recommended.
Herbal Products		

St. John's wort (*Hypericum perforatum*)	↓ letermovir	Co-administration of PREVYMIS with St. John's wort may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and St. John's wort is not recommended.
HIV Medications		
efavirenz	↓ letermovir	Co-administration of PREVYMIS with efavirenz may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and efavirenz is not recommended.
etravirine	↓ letermovir	Co-administration of PREVYMIS with etravirine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and etravirine is not recommended.
nevirapine	↓ letermovir	Co-administration of PREVYMIS with nevirapine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and nevirapine is not recommended.
HMG-CoA Reductase Inhibitors		
atorvastatin‡	↑ atorvastatin	Co-administration of PREVYMIS with atorvastatin increases plasma concentrations of atorvastatin. Statin-associated adverse events such as myopathy should be closely monitored. The dose of atorvastatin should not exceed 20 mg daily when co-administered with PREVYMIS§.
pitavastatin, simvastatin	↑ pitavastatin ↑ simvastatin	Co-administration of PREVYMIS and pitavastatin or simvastatin is not recommended. When PREVYMIS is co-administered with cyclosporine, use of either pitavastatin or simvastatin is contraindicated *[see 3 CONTRAINDICATIONS].*
Other HMG-CoA reductase inhibitors Examples: fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ concentrations of HMG-CoA reductase inhibitors	PREVYMIS may increase statin plasma concentrations. Statin-associated adverse events such as myopathy should be closely monitored. A dose adjustment may be necessary when co-administered with PREVYMIS§.
Immunosuppressants		

cyclosporine‡	↑ cyclosporine ↑ letermovir	Co-administration of PREVYMIS with cyclosporine increases concentrations of both letermovir and cyclosporine. If PREVYMIS is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor), the dosage of PREVYMIS should be decreased to 240 mg once daily *[see 2 DOSAGE AND ADMINISTRATION, 2.3 Dosage Adjustment in Adults]*. Frequent monitoring of cyclosporine whole blood concentrations should be performed during and at discontinuation of PREVYMIS and the dose of cyclosporine adjusted accordingly§.
sirolimus‡	↑ sirolimus	Co-administration of PREVYMIS with sirolimus increases concentrations of sirolimus. Frequent monitoring of sirolimus whole blood concentrations should be performed during and at discontinuation of PREVYMIS and the dose of sirolimus adjusted accordingly§.
tacrolimus‡	↑ tacrolimus	Co-administration of PREVYMIS with tacrolimus increases tacrolimus plasma concentrations. Frequent monitoring of tacrolimus whole blood concentrations should be performed during and at discontinuation of PREVYMIS and the dose of tacrolimus adjusted accordingly§.
Proton pump inhibitors		
omeprazole, pantoprazole	↓ omeprazole ↓ pantoprazole	Co-administration of PREVYMIS with these proton pump inhibitors (PPI) may decrease plasma concentrations of the PPIs. Clinical monitoring and dose adjustment may be needed when co-administered with PREVYMIS§.
Wakefulness-Promoting Agents		
modafinil	↓ letermovir	Co-administration of PREVYMIS with modafinil may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and modafinil is not recommended.
CYP2C8 Substrates¶		
Examples: repaglinide rosiglitazone	↑ concentrations of CYP2C8 substrates	PREVYMIS may increase the plasma concentrations of CYP2C8 substrates. Frequent monitoring of glucose concentrations is recommended during co-administration of repaglinide or rosiglitazone§.
CYP3A Substrates		

Examples: alfentanil, fentanyl, midazolam‡, quinidine	↑ concentrations of CYP3A substrate	PREVYMIS may increase the plasma concentrations of CYP3A substrates. When PREVYMIS is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor§. Frequent monitoring for adverse reactions related to these agents is recommended during co-administration. Dose adjustment of CYP3A substrates may be needed§ *[see 4 WARNINGS AND PRECAUTIONS, 4.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions]*.
* This table is not all inclusive. † ↓=decrease, ↑=increase ‡ These interactions have been studied. § Refer to the respective prescribing information. ¶ Based on physiologically based pharmacokinetic modeling.		

5.4 Drugs without Clinically Significant Interactions with PREVYMIS

There was no clinically relevant interaction when PREVYMIS was co-administered with itraconazole, a P-gp/BCRP inhibitor.

There were no clinically relevant changes in plasma concentrations of digoxin, a P-gp substrate, and acyclovir, an OAT3 substrate, following co-administration with PREVYMIS in clinical studies.

The interaction between letermovir and the following drugs was evaluated in clinical studies: mycophenolate mofetil, fluconazole, posaconazole, and oral contraceptives. No dose adjustments are needed when PREVYMIS is used with these drugs.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

No adequate human data are available to establish whether or not PREVYMIS poses a risk to pregnancy outcomes. Embryofetal toxicity was observed in rats and rabbits at maternally toxic systemic AUC exposures of approximately 11- and 2-fold, respectively, the AUC at the recommended human dose (RHD). In the rat pre-and post-natal development study, no developmental toxicity was observed up to the highest maternal systemic AUC exposure (approximately 2-fold the AUC at the RHD). For the purpose of calculating safety margins, the AUC at the RHD is defined as the mean AUC in HSCT recipients receiving 480 mg IV.

The background risk of major birth defects and miscarriage for the indicated population is unknown. The potential risk for humans is unknown. PREVYMIS should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

6.2 Nursing Mothers

It is not known whether letermovir is present in human breast milk, affects human milk production, or has effects on the breastfed child.

When administered to lactating rats, letermovir was present in milk, without effects on growth and development in nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREVYMIS and any potential adverse effects on the breastfed child from PREVYMIS or from the underlying maternal condition.

6.3 Fertility

There were no effects on female fertility in rats. Impairment of fertility was observed in male rats, but not in male mice or male monkeys. Testicular toxicity in rats appears to be species-specific, and the relevance to humans is unknown. In the Phase 3 trial in HSCT recipients, there was no evidence of letermovir-related testicular toxicity *[see 7 ADVERSE REACTIONS, 7.1 Clinical Trials Experience].*

6.4 Pediatric Use

Safety and efficacy of PREVYMIS in patients below 18 years of age have not been established.

6.5 Geriatric Use

Safety and efficacy were similar across older and younger subjects in the Phase 3 trial in HSCT recipients.

6.6 Renal Impairment

No dose adjustment of PREVYMIS is required based on renal impairment *[see 2 DOSAGE AND ADMINISTRATION, 2.6 Renal Impairment, 2.7 Hepatic Impairment, and 6 USE IN SPECIFIC POPULATIONS, 6.7 Hepatic Impairment].* There are no data in patients with end-stage renal disease (CrCl less than 10 mL/min), including patients on dialysis.

In patients with moderate or severe renal impairment (CrCl less than 50 mL/min) receiving PREVYMIS concentrate for solution for infusion, accumulation of the intravenous vehicle, hydroxypropyl betadex, could occur. Serum creatinine levels should be closely monitored in these patients.

6.7 Hepatic Impairment

No dose adjustment of PREVYMIS is required based on mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment *[see 2 DOSAGE AND ADMINISTRATION, 2.7 Hepatic Impairment]*.

PREVYMIS is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment *[see 2 DOSAGE AND ADMINISTRATION, 2.7 Hepatic Impairment]*.

7. ADVERSE REACTIONS

7.1 Clinical Trials Experience

Adults

Adult CMV-seropositive Recipients [R+] of an Allogeneic HSCT

The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, placebo-controlled trial (P001) in which 565 subjects were randomized and treated with PREVYMIS (N=373) or placebo (N=192) through Week 14 post-transplant and were followed for safety through Week 24 post-transplant.

Cardiac Adverse Events:

The cardiac adverse event rate (regardless of investigator-assessed causality) was higher in subjects receiving PREVYMIS (13%) compared to subjects receiving placebo (6%). The most common cardiac adverse events were tachycardia (reported in 4% of PREVYMIS subjects and in 2% of placebo subjects) and atrial fibrillation (reported in 3% of PREVYMIS subjects and in 1% of placebo subjects).

Among those subjects who experienced one or more cardiac adverse events, 85% of PREVYMIS and 92% of placebo subjects had events reported as mild or moderate in severity.

The most commonly reported adverse reactions occurring in at least 1% of subjects in the PREVYMIS group through Week 24 post-transplant and at a frequency greater than placebo were: nausea, diarrhea, and vomiting (Table 2).

Table 2: P001 Adverse Reactions Reported in ≥1% HSCT Recipients in the PREVYMIS Group and at a Frequency Greater than Placebo Through Week 24 Post-Transplant

Adverse Reaction	PREVYMIS (N=373)	Placebo (N=192)
nausea	7.2%	3.6%
diarrhea	2.4%	1.0%
vomiting	1.9%	1.0%

Hypersensitivity was reported as a non-serious adverse reaction with PREVYMIS in one subject.

Overall, similar proportions of subjects in each group discontinued study medication due to an adverse reaction (4.8% PREVYMIS vs. 3.6% placebo). The most frequently reported adverse reactions that led to discontinuation of PREVYMIS were nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%).

Laboratory Abnormalities
Overall, the percentage of subjects with potentially clinically significant changes in laboratory values (e.g., hematology, chemistry, renal, and hepatic function) was similar in the PREVYMIS and placebo groups. There were no differences in the incidence of or time to engraftment between the PREVYMIS and placebo groups.

Biomarkers of testicular toxicity were evaluated in male subjects in P001. The changes from baseline in male sex hormones (serum inhibin B, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone) were similar in the PREVYMIS and placebo groups.

8. OVERDOSAGE

During Phase 1 clinical trials, 86 healthy subjects received doses ranging from 720 mg/day to 1440 mg/day of PREVYMIS for up to 14 days. The adverse reaction profile was similar to that of the clinical dose of 480 mg/day. There is no specific antidote for overdose with PREVYMIS. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment instituted.

It is unknown whether dialysis will result in meaningful removal of PREVYMIS from systemic circulation.

9. CLINICAL STUDIES

Adult CMV-seropositive Recipients [R+] of an Allogeneic Hematopoietic Stem Cell Transplant
To evaluate PREVYMIS prophylaxis as a preventive strategy for CMV infection or disease in transplant recipients at high risk for CMV reactivation, the efficacy of PREVYMIS was assessed in a multicenter, double-blind, placebo-controlled Phase 3 trial (P001) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Subjects were randomized (2:1) to receive either PREVYMIS at a dose of 480 mg once daily adjusted to 240 mg when co-administered with cyclosporine, or placebo.

Randomization was stratified by investigational site and risk level for CMV reactivation at the time of study entry. Study drug was initiated after HSCT (Day 0-28 post-transplant) and continued through Week 14 post-transplant. Study drug was administered either orally or IV; the dose of PREVYMIS was the same regardless of the route of administration. Subjects were monitored through Week 24 post-transplant for the primary efficacy endpoint with continued follow-up through Week 48 post-transplant.

Among the 565 treated subjects, 373 subjects received PREVYMIS (including 99 subjects who received at least one IV dose) and 192 received placebo (including 48 subjects who received at least one IV dose). The median time to starting study drug was 9 days after transplantation. Thirty-seven percent (37%) of subjects were engrafted at baseline. The median age was 54 years (range: 18 to 78 years); 58% were male; 82% were White; 10% were Asian; 2% were Black or African; and 7% were Hispanic or Latino. At baseline, 50% of subjects received a myeloablative regimen, 52% were receiving cyclosporine, and 42% were receiving tacrolimus. The most common primary reasons for transplant were acute myeloid leukemia (38%), myeloblastic syndrome (15%), and lymphoma (13%). Twelve percent (12%) of subjects were positive for CMV DNA at baseline.

At baseline, 31% of subjects were in the high risk stratum as defined by one or more of the following criteria: Human Leukocyte Antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR, haploidentical donor; unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1; use of umbilical cord blood as stem cell source; use of *ex vivo* T-cell-depleted grafts; Grade 2 or greater Graft-Versus-Host Disease (GVHD), requiring systemic corticosteroids. The remaining 69% of subjects did not meet any of these high risk stratum criteria and were therefore included in the low risk stratum.

Efficacy

Clinically Significant CMV Infection

The primary efficacy endpoint of P001 was the incidence of clinically significant CMV infection through Week 24 post-transplant. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viremia (using the Roche COBAS® AmpliPrep/COBAS TaqMan® assay, LLoQ is 137 IU/mL, which is approximately 150 copies/mL) and the clinical condition of the subject. The Non-Completer=Failure (NC=F) approach was used, where subjects who discontinued from the study prior to Week 24 post-transplant or had a missing outcome at Week 24 post-transplant were counted as failures.

PREVYMIS demonstrated superior efficacy over placebo in the analysis of the primary endpoint, as shown in Table 3. The estimated treatment difference of -23.5% was statistically significant (one-sided p-value <0.0001).

Table 3: P001 Efficacy Results in HSCT Recipients (NC=F Approach, FAS Population)

Parameter	PREVYMIS (N=325) n (%)	Placebo (N=170) n (%)
Primary Endpoint (Proportion of subjects who failed prophylaxis)	**122 (37.5)**	**103 (60.6)**
Reasons for Failures*		
Clinically significant CMV infection by Week 24†	57 (17.5)	71 (41.8)
Initiation of PET based on documented CMV viremia	52 (16.0)	68 (40.0)
CMV end-organ disease	5 (1.5)	3 (1.8)

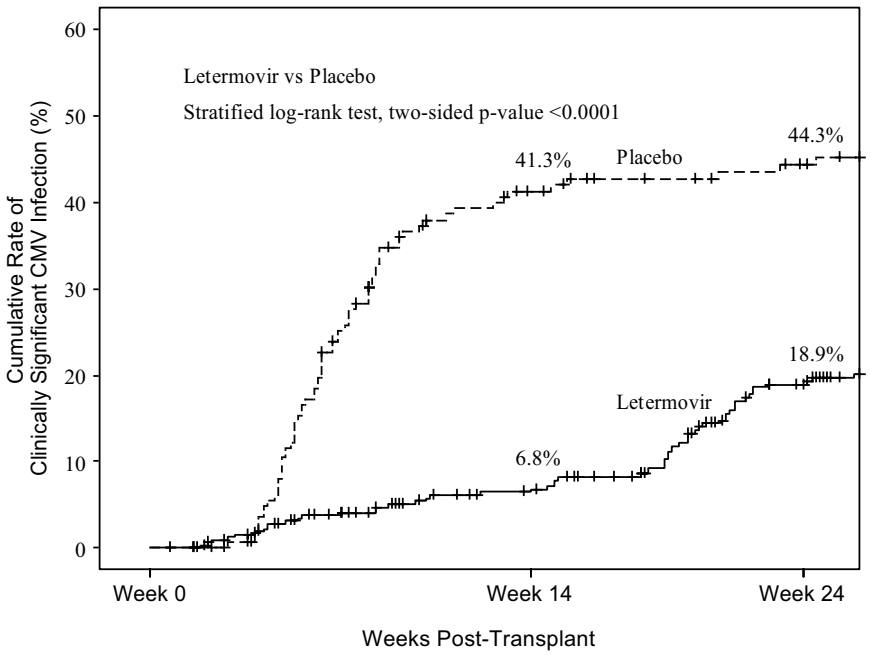
Discontinued from study before Week 24	56 (17.2)	27 (15.9)
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)
Stratum-adjusted treatment difference (PREVYMIS-Placebo)‡		
Difference (95% CI)	-23.5 (-32.5, -14.6)	
p-value	<0.0001	

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
† Clinically significant CMV infection was defined as CMV end-organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the subject.
‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A 1-sided p-value ≤0.0249 was used for declaring statistical significance.
Note: FAS=Full analysis set; FAS includes randomized subjects who received at least one dose of study medication, and excludes subjects with detectable CMV DNA at baseline.
Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.
N = number of subjects in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

At Week 24 post-transplant, the Kaplan-Meier (K-M) event rate for clinically significant CMV infection was 18.9% in the PREVYMIS group compared to 44.3% in the placebo group (nominal two-sided stratified log-rank p-value<0.0001) (see Figure 1). Factors associated with clinically significant CMV infection between Week 14 and Week 24 post-transplant among PREVYMIS-treated subjects included high risk for CMV reactivation at baseline, having GVHD, and steroid use at any time after randomization.

Of the 373 subjects treated with PREVYMIS in P001, 56 (15.0%) subjects were 65 years of age or older. Safety and efficacy were similar across older and younger subjects.

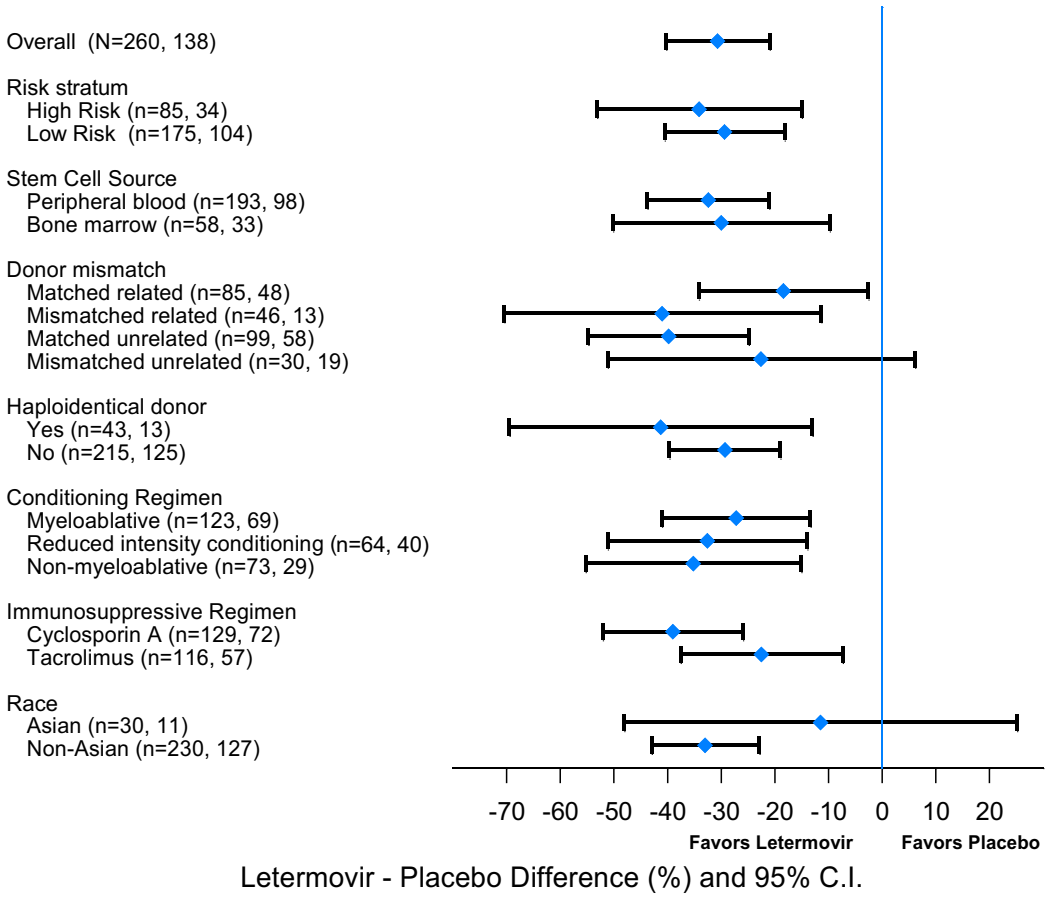
Figure 1: P001: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 Post-Transplant in HSCT Recipients (FAS Population)



Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

Efficacy consistently favored PREVYMIS across subgroups including low and high risk strata for CMV reactivation, conditioning regimens, and concomitant immunosuppressive regimens.

Figure 2: P001 Forest Plot of the Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Selected Subgroups (DAO Approach, FAS Population)

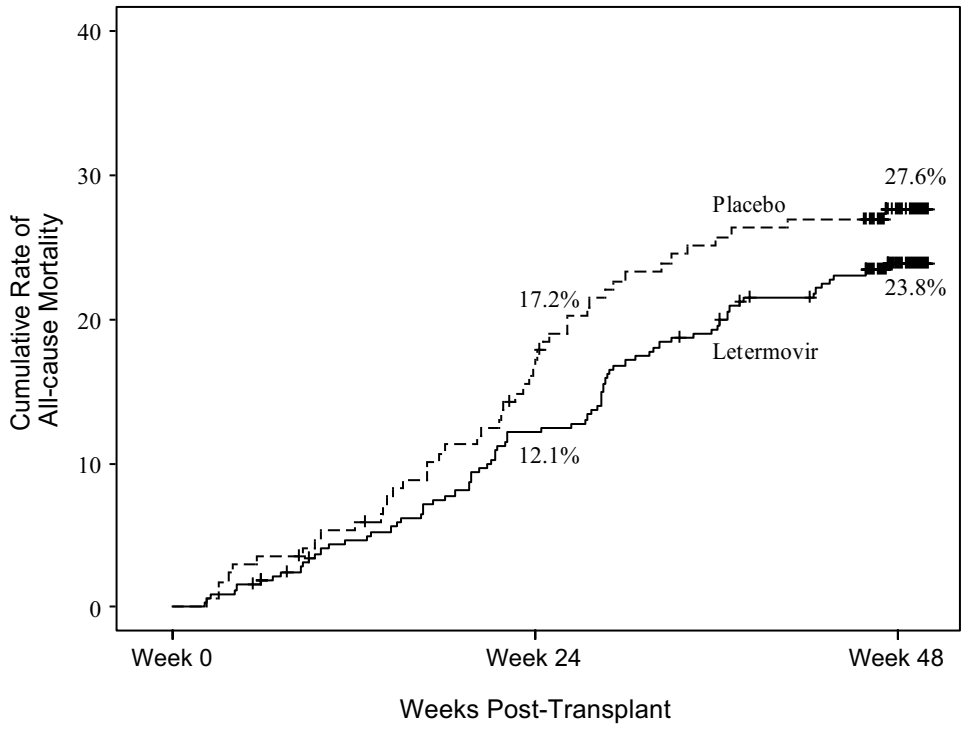


DAO= data as observed. With DAO approach, any subject with a missing value was excluded from the analysis.

Mortality

The K-M event rate for all-cause mortality in the letermovir vs. placebo groups was 12.1% vs. 17.2% at Week 24 post-transplant (nominal two-sided stratified log-rank p-value=0.0401), and 23.8% vs. 27.6% at Week 48 post-transplant (nominal two-sided stratified log-rank p-value=0.2117; see Figure 3).

Figure 3: P001: Kaplan-Meier Plot of Time to All-Cause Mortality Through Week 48 Post-Transplant in HSCT Recipients (FAS Population)



Number of Subjects at Risk			
Letermovir	325	282	165
Placebo	170	139	81

In a post-hoc analysis of all-cause mortality through Week 48 post-transplant, among subjects with clinically significant CMV infection through Week 24, the mortality rate in the letermovir vs. placebo groups was 21.1% vs. 33.8%; and among subjects without clinically significant CMV infection through Week 24, the mortality rate in the letermovir vs. placebo groups was 23.9% vs. 22.2%.

10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class
PREVYMIS is an antiviral drug.

10.2 Mechanism of Action
PREVYMIS is an antiviral drug against CMV *[see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacodynamics]*.

10.3 Pharmacodynamics
Cardiac Electrophysiology

The effect of letermovir on doses up to 960 mg given IV on the QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg oral) 4-period crossover thorough QT trial in 38 healthy subjects. Letermovir does not prolong QTc to any clinically relevant extent following the 960 mg IV dose, with plasma concentrations approximately 2-fold higher than the 480 mg IV dose.

Microbiology

Mechanism of Action

Letermovir inhibits the CMV DNA terminase complex, which is required for viral replication. Biochemical characterization and electron microscopy demonstrated that letermovir affects the formation of proper unit length genomes and interferes with virion maturation.

Antiviral Activity

The median EC_{50} value of letermovir against a collection of clinical CMV isolates in a cell-culture model of infection was 2.1 nM (range = 0.7 nM to 6.1 nM, n=74).

Viral Resistance

In Cell Culture

The CMV genes UL51, UL56, and UL89 encode subunits of CMV DNA terminase. CMV mutants with reduced susceptibility to letermovir have been selected in cell culture, and the substitutions map to pUL51 (P91S, A95V), pUL56 (C25F, S229F, V231A, V231L, N232Y, V236A, V236L, V236M, E237D, L241P, T244K, T244R, L254F, L257F, L257I, K258E, F261C, F261L, F261S, Y321C, C325F, C325R, C325W, C325Y, L328V, M329T, A365S, N368D, R369G, R369M, R369S), and pUL89 (N320H, D344E). EC_{50} values for recombinant CMV mutants expressing these substitutions are 1.6- to 9,300-fold higher than those for the wild-type reference virus.

In Clinical Studies

In a Phase 2b trial evaluating letermovir doses of 60, 120, or 240 mg/day or placebo for up to 84 days in 131 HSCT recipients, DNA sequence analysis of a select region of UL56 (amino acids 231 to 369) was performed on samples obtained from 12 letermovir-treated subjects who experienced prophylaxis failure and for whom samples were available for analysis. One subject (who received 60 mg/day) had a letermovir resistant genotypic variant (GV) (V236M).

In a Phase 3 trial (P001), DNA sequence analysis of the entire coding regions of UL56 and UL89 was performed on samples obtained from 40 letermovir-treated subjects in the FAS population who experienced prophylaxis failure and for whom samples were available for analysis. A total of 2 letermovir resistance-associated substitutions both mapping to pUL56 were detected in 2 subjects. One subject had the substitution V236M, and the other had E237G.

Cross Resistance

Cross resistance is not likely with drugs outside of this class. Letermovir is fully active against viral populations with substitutions conferring resistance to CMV DNA polymerase inhibitors (ganciclovir, cidofovir, and foscarnet). A panel of recombinant CMV strains with substitutions conferring resistance to letermovir was fully susceptible to cidofovir, foscarnet and ganciclovir with the exception of a recombinant strain with the pUL56 E237G substitution which confers a 2.1-fold reduction in ganciclovir susceptibility relative to wild-type.

Pharmacogenomics

The impact of genetic variants in the OATP1B1 gene SLCO1B1 (rs4149056, rs2306283, rs4149032) and UGT1A1 (rs4148323 and the promoter TA repeat variants) on the pharmacokinetics of letermovir was evaluated in 299 study participants. There was no clinically relevant impact of these variants on letermovir exposures.

10.4 Pharmacokinetics

General Introduction

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

In healthy subjects, letermovir exposure increased in a greater than dose-proportional manner with both oral or IV administration following single and multiple doses of 240 mg and 480 mg. Letermovir

was absorbed rapidly with a median time to maximum plasma concentration (T_{max}) of 1.5 to 3.0 hours and declined in a biphasic manner. The geometric mean steady-state AUC and C_{max} values were 71,500 ng•hr/mL and 13,000 ng/mL, respectively, with 480 mg once daily oral PREVYMIS. The post-absorption plasma concentration-time profile of letermovir following oral administration was similar to the profile observed with IV dosing. Letermovir clearance (CL) reached steady-state in 9 to 10 days with an accumulation ratio of 1.22 for AUC and 1.03 for C_{max}.

In HSCT recipients, letermovir AUC was estimated using population pharmacokinetic analyses using Phase 3 data (see Table 4). Differences in exposure across treatment regimens are not clinically relevant; efficacy was consistent across the range of exposures observed in P001.

Table 4: Letermovir AUC (ng•hr/mL) Values in HSCT Recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	34,400 (16,900, 73,700)
480 mg IV, no cyclosporine	100,000 (65,300, 148,000)
240 mg Oral, with cyclosporine	60,800 (28,700, 122,000)
240 mg IV, with cyclosporine	70,300 (46,200, 106,000)
* Medians and 90% prediction intervals are based on simulations using the Phase 3 population PK model with inter-individual variability.	

Absorption

In healthy subjects, absolute bioavailability of letermovir was estimated to be approximately 94% over the dose range 240 mg to 480 mg based on population pharmacokinetic analyses. In HSCT recipients, bioavailability of letermovir was estimated to be approximately 35% with 480 mg once daily oral PREVYMIS administered without cyclosporine. The inter-individual variability for bioavailability was estimated to be approximately 37%.

Effect of Cyclosporine

In HSCT recipients, co-administration of cyclosporine increased plasma concentrations of letermovir. Bioavailability of letermovir was estimated to be approximately 85% with 240 mg once daily oral PREVYMIS co-administered with cyclosporine. If PREVYMIS is co-administered with cyclosporine, the recommended dose of PREVYMIS is 240 mg once daily *[see 2 DOSAGE AND ADMINISTRATION, 2.3 Dosage Adjustment in Adults]*.

Effect of Food

Relative to fasting conditions, oral administration of 480 mg single dose of PREVYMIS with a standard high fat and high calorie meal did not have any effect on the overall exposure (AUC) and resulted in approximately 30% increase in peak levels (C_{max}) of letermovir. PREVYMIS may be administered orally with or without food *[see 2 DOSAGE AND ADMINISTRATION, 2.1 General]*.

Distribution

Based on population pharmacokinetic analyses, the mean steady-state volume of distribution is estimated to be 45.5 L following IV administration in HSCT recipients.

Letermovir is extensively bound (98.7%) to human plasma proteins *in vitro*. Blood to plasma partitioning of letermovir is 0.56 and independent of the concentration range (0.1 to 10 mg/L) evaluated *in vitro*.

In preclinical distribution studies, letermovir is distributed to organs and tissues with the highest concentrations observed in the gastrointestinal tract, bile duct and liver and low concentrations in the brain.

Elimination

The mean apparent terminal half-life for letermovir is approximately 12 hours with 480 mg IV PREVYMIS in healthy subjects.

Metabolism
The majority of drug-related component in plasma is unchanged parent (96.6%). No major metabolites are detected in plasma. Letermovir is partly eliminated by glucuronidation mediated by UGT1A1/1A3.

Excretion
Based on population pharmacokinetic analyses, letermovir steady-state CL is estimated to be 4.84 L/hr following IV administration in HSCT recipients. The inter-individual variability for CL is estimated to be 24.6%.

After oral administration of radio-labeled letermovir, 93.3% of radioactivity was recovered in feces. The majority of drug was excreted as unchanged parent with a minor amount (6% of dose) as an acyl-glucuronide metabolite in feces. Urinary excretion of letermovir was negligible (<2% of dose).

Specific Populations
Pediatric Population
The pharmacokinetics of letermovir in pediatric patients less than 18 years of age have not been evaluated.

Geriatric Population
Based on population pharmacokinetic analyses, there is no effect of age on letermovir pharmacokinetics. No dose adjustment is required based on age.

Gender
Based on population pharmacokinetic analyses, there is no difference in letermovir pharmacokinetics in females compared to males.

Weight
Based on population pharmacokinetic analyses, letermovir AUC is estimated to be 18.7% lower in subjects weighing 80-100 kg compared to subjects weighing 67 kg. This change is not clinically relevant.

Race
Based on population pharmacokinetic analyses, letermovir AUC is estimated to be 33.2% higher in Asians compared to Whites. This change is not clinically relevant.

Renal Impairment
Letermovir AUC was approximately 1.9- and 1.4-fold higher in subjects with moderate (eGFR greater than or equal to 30 to 59 mL/min/1.73 m^2) and severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment, respectively, compared to healthy subjects. The changes in letermovir exposure due to renal impairment are not clinically relevant.

Hepatic Impairment
Letermovir AUC was approximately 1.6- and 3.8-fold higher in subjects with moderate (Child-Pugh Class B [CP-B], score of 7-9) and severe (Child-Pugh Class C [CP-C], score of 10-15) hepatic impairment, respectively, compared to healthy subjects. The changes in letermovir exposure in subjects with moderate hepatic impairment are not clinically relevant.

Clinically relevant increases in letermovir exposure are anticipated in patients with severe hepatic impairment or in patients with moderate hepatic impairment combined with moderate or severe renal impairment.

10.5 Drug Interaction Studies

Drug interaction studies were performed in healthy subjects with PREVYMIS and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions (see Table 5 and Table 6).

In vitro results indicate that letermovir is a substrate of OATP1B1/3, P-gp, UGT1A1, and UGT1A3. Inhibitors of OATP1B1/3 transporters may result in increases in letermovir plasma concentrations. If PREVYMIS is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor), the recommended dose of PREVYMIS is 240 mg once daily *[see 2 DOSAGE AND ADMINISTRATION, 2.3 Dosage Adjustment in Adults]*. Changes in letermovir plasma concentrations due to inhibition of P-gp/BCRP by itraconazole were not clinically relevant. Inhibition of UGTs is not anticipated to have a clinically relevant effect on letermovir plasma concentrations. Induction of drug enzymes (e.g., UGTs) and/or transporters (e.g., P-gp) by rifampin may result in clinically relevant decreases in letermovir plasma concentrations; therefore, co-administration of strong and moderate inducers with letermovir is not recommended *[see 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.1 Effects of Other Drugs on PREVYMIS],* Table 1, and Table 5. Although CYP3A, CYP2D6 and CYP2J2 were identified as enzymes capable of mediating the metabolism of letermovir *in vitro*, oxidative metabolism is considered to be a minor elimination pathway based on *in vivo* human data.

Letermovir is a time-dependent inhibitor and inducer of CYP3A *in vitro*. Co-administration of PREVYMIS with midazolam resulted in increased exposure of midazolam, indicating that the net effect of letermovir on CYP3A is moderate inhibition (see Table 6). Based on these results, co-administration of PREVYMIS with CYP3A substrates may increase the plasma concentrations of the CYP3A substrates *[see 3 CONTRAINDICATIONS, 4 WARNINGS AND PRECAUTIONS, 4.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions, and 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 Effects of PREVYMIS on Other Drugs, and 5.3 Established and Other Potential Drug Interactions]* and Table 1. Letermovir is a reversible inhibitor of CYP2C8 *in vitro*. Physiologically based pharmacokinetic modeling predicts an increase in plasma concentrations of CYP2C8 substrates when co-administered with PREVYMIS *[see Table 1 in 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Established and Other Potential Drug Interactions].* Co-administration of PREVYMIS reduced the exposure of voriconazole, most likely due to the induction of voriconazole elimination pathways, CYP2C9 and CYP2C19. Co-administration of PREVYMIS with CYP2C9 and CYP2C19 substrates may decrease the plasma concentrations of the CYP2C9 and CYP2C19 substrates *[see Table 1 in 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Established and Other Potential Drug Interactions].* Letermovir is an inducer of CYP2B6 *in vitro*; the clinical relevance is unknown.

Letermovir inhibited efflux transporters P-gp, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), multidrug resistance-associated protein 2 (MRP2), OAT3, and hepatic uptake transporter OATP1B1/3 *in vitro*. Co-administration of PREVYMIS with substrates of OATP1B1/3 transporters (e.g., atorvastatin, a known substrate of CYP3A, OATP1B1/3, and potentially BCRP) may result in a clinically relevant increase in plasma concentrations of OATP1B1/3 substrates *[see Table 1 in 5 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Established and Other Potential Drug Interactions].* There were no clinically relevant changes in plasma concentrations of digoxin, a P-gp substrate, or acyclovir, an OAT3 substrate, following co-administration with PREVYMIS in clinical studies (see Table 6). The effect of letermovir on BCRP, BSEP, and MRP2 substrates was not evaluated in clinical studies; the clinical relevance is unknown.

Table 5: Drug Interactions: Changes in Pharmacokinetics of Letermovir in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	N	Geometric Mean Ratio [90% CI] of Letermovir PK with/without Co-administered Drug (No Effect=1.00)	
				AUC	Cmax
Antifungal Agents					
fluconazole	400 mg single dose PO	480 mg single dose PO	14	1.11 (1.01, 1.23)	1.06 (0.93, 1.21)
itraconazole	200 mg once daily PO	480 mg once daily PO	14	1.33 (1.17, 1.51)	1.21 (1.05, 1.39)
Antimycobacterials					
rifampin	600 mg single dose PO	480 mg single dose PO	16	2.03 (1.84, 2.26)	1.59 (1.46, 1.74)
	600 mg single dose IV	480 mg single dose PO	16	1.58 (1.38, 1.81)	1.37 (1.16, 1.61)
	600 mg once daily PO*	480 mg once daily PO	14	0.81 (0.67, 0.98)	1.01 (0.79, 1.28)
	600 mg once daily PO (24 hours after rifampin)†	480 mg once daily PO	14	0.15 (0.13, 0.17)	0.27 (0.22, 0.31)
Immunosuppressants					
cyclosporine	200 mg single dose PO	240 mg once daily PO	12	2.11 (1.97, 2.26)	1.48 (1.33, 1.65)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	14	1.18 (1.04, 1.32)	1.11 (0. 92, 1.34)
tacrolimus	5 mg single dose PO	80 mg twice daily PO	14	1.02 (0.97, 1.07)	0.92 (0.84, 1.00)

Abbreviations: PO= oral

*C24 GMR [90%] is 0.14 (0.11, 0.19)

†These data are the effect of rifampin on letermovir 24 hours after final rifampin dose. C24 GMR [90%] is 0.09 (0.06, 0.12).

Table 6: Drug Interactions: Changes in Pharmacokinetics for Co-administered Drug in the Presence of Letermovir or Co-administered Letermovir

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	N	Geometric Mean Ratio [90% CI] of Co-administered Drug PK with/without Letermovir (No Effect=1.00)	
				AUC	Cmax
CYP3A Substrates					
midazolam	1 mg single dose IV	240 mg once daily PO	16	1.47 (1.37, 1.58)	1.05 (0.94, 1.17)

	2 mg single dose PO	240 mg once daily PO	16	2.25 (2.04, 2.48)	1.72 (1.55, 1.92)
P-gp Substrates					
digoxin	0.5 mg single dose PO	240 mg twice daily PO	22	0.88 (0.80, 0.96)	0.75 (0.63, 0.89)
Immunosuppressants					
cyclosporine	50 mg single dose PO	240 mg once daily PO	14	1.66 (1.51, 1.82)	1.08 (0.97, 1.19)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	14	1.08 (0.97, 1.20)	0.96 (0.82, 1.12)
tacrolimus	5 mg single dose PO	480 mg once daily PO	13	2.42 (2.04, 2.88)	1.57 (1.32, 1.86)
sirolimus	2 mg single dose PO	480 mg once daily PO	13	3.40 (3.01, 3.85)	2.76 (2.48, 3.06)
Antifungal and Antiviral Agents					
acyclovir	400 mg single dose PO	480 mg once daily PO	13	1.02 (0.87, 1.2)	0.82 (0.71, 0.93)
fluconazole	400 mg single dose PO	480 mg single dose PO	14	1.03 (0.99, 1.08)	0.95 (0.92, 0.99)
itraconazole	200 mg once daily PO	480 mg once daily PO	14	0.76 (0.71, 0.81)	0.84 (0.76, 0.92)
posaconazole	300 mg single dose PO	480 mg once daily PO	13	0.98 (0.82, 1.17)	1.11 (0.95, 1.29)
voriconazole	200 mg twice daily PO	480 mg once daily PO	12	0.56 (0.51, 0.62)	0.61 (0.53, 0.71)
HMG-CoA Reductase Inhibitors					
atorvastatin	20 mg single dose PO	480 mg once daily PO	14	3.29 (2.84, 3.82)	2.17 (1.76, 2.67)
Oral Contraceptives					
ethinyl estradiol (EE) /levonorgestrel (LNG)	0.03 mg EE single dose PO	480 mg once daily PO	22	1.42 (1.32, 1.52)	0.89 (0.83, 0.96)
	0.15 mg LNG single dose PO		22	1.36 (1.30, 1.43)	0.95 (0.86, 1.04)
Abbreviations: PO=oral					

11. ANIMAL TOXICOLOGY

11.1 General Toxicity

Testicular toxicity was noted only in rats at systemic exposures (AUC) ≥3-fold the exposures in humans at the RHD. This toxicity was characterized by seminiferous tubular degeneration, and oligospermia and cell debris in the epididymides, with decreased testicular and epididymides weights. The No-Observed Adverse Effect Level (NOAEL) for testicular toxicity in rats was observed at exposures (AUC) in rats similar to the exposures in humans at the RHD. This testicular toxicity appears to be species-specific; testicular toxicity was not observed in mice and monkeys at the

highest doses tested at exposures up to 4-fold and 2-fold, respectively, the exposures in humans at the RHD. The relevance to humans is unknown. In the Phase 3 trial in HSCT recipients, there was no evidence of letermovir-related testicular toxicity *[see 7 ADVERSE REACTIONS, 7.1 Clinical Trials Experience]*.

The toxicity profile of letermovir was generally similar in oral and intravenous studies in rats and monkeys, with the exception of vacuolation noted in the kidneys of rats administered IV letermovir formulated with 1500 mg/kg/day of the cyclodextrin excipient hydroxypropyl betadex. It is known that hydroxypropyl betadex can cause kidney vacuolation in rats when given intravenously at doses greater than 50 mg/kg/day {1}.

11.2 Carcinogenesis

A 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice showed no evidence of human-relevant tumorigenesis up to the highest doses tested, 150 mg/kg/day and 300 mg/kg/day in males and females, respectively.

11.3 Mutagenesis

Letermovir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis assays, chromosomal aberration in Chinese Hamster Ovary cells, and in an *in vivo* mouse micronucleus study.

11.4 Reproduction

In the fertility and early embryonic development studies in the rat, there were no effects of letermovir on female fertility at the highest dose tested, 240 mg/kg/day (approximately 5-fold the AUC in humans at the RHD). In male rats, reduced sperm concentration, reduced sperm motility, and decreased fertility were observed at systemic exposures ≥ 3-fold the AUC in humans at the RHD *[see 11 ANIMAL TOXICOLOGY, 11.1 General Toxicity]*.

In male mice, there were no effects on testicular toxicity by histopathologic evaluation at systemic exposures approximately 4-fold the AUC in humans at the RHD.

In a study dedicated to investigate effects on the male reproductive system of mature monkeys administered letermovir, there was no evidence of testicular toxicity based on histopathologic evaluation, measurement of testicular size, blood hormone analysis (follicle stimulating hormone, inhibin B and testosterone) and sperm evaluation (sperm count, motility and morphology) at systemic exposures approximately 2-fold the AUC in humans at the RHD.

11.5 Development

Letermovir was administered orally to pregnant rats at 0, 10, 50 or 250 mg/kg/day from gestation days 6 to 17. Maternal toxicity (including decrease in body weight gain) was noted at 250 mg/kg/day (approximately 11-fold the AUC at the RHD); in the offspring, decreased fetal weight with delayed ossification, slightly edematous fetuses, and increased incidence of shortened umbilical cords and of variations and malformations in the vertebrae, ribs, and pelvis were observed. No maternal or developmental effects were noted at the dose of 50 mg/kg/day (approximately 2.5-fold the AUC at the RHD).

Letermovir was administered orally to pregnant rabbits at 0, 25, 75 or 225 mg/kg/day from gestation days 6 to 20. Maternal toxicity (including mortality and abortions) was noted at 225 mg/kg/day (approximately 2-fold the AUC at the RHD); in the offspring, an increased incidence of malformations and variations in the vertebrae and ribs were observed. No maternal or developmental effects were noted at the dose of 75 mg/kg/day (at less than the AUC at the RHD).

In the pre- and post-natal developmental study, letermovir was administered orally to pregnant rats at 0, 10, 45 or 180 mg/kg/day from gestation day 6 to lactation day 22. There was no developmental toxicity observed up to the highest exposure tested (2-fold the AUC at the RHD).

12. NAME OF THE DRUG

PREVYMIS

13. PHARMACEUTICAL FORM

13.1 Tablet

PREVYMIS 240 mg tablet is a yellow oval tablet. Each tablet is debossed with “591” on one side and corporate logo on the other side.

PREVYMIS 480 mg tablet is a pink oval, bi-convex tablet. Each tablet is debossed with “595” on one side and corporate logo on the other side.

13.2 Concentrate for Solution for Infusion

PREVYMIS 240 mg/12 mL (20 mg/mL) concentrate for solution for infusion is supplied as a clear solution in a single-dose vial.

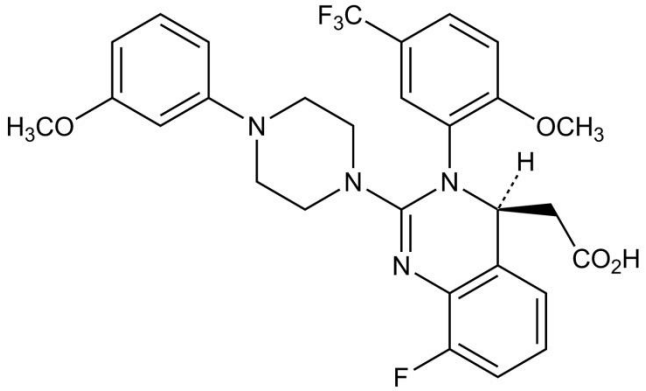
PREVYMIS 480 mg/24 mL (20 mg/mL) concentrate for solution for infusion is supplied as a clear solution in a single-dose vial.

14. PHARMACEUTICAL PARTICULARS

14.1 Chemistry

Letermovir has a molecular formula of $C_{29}H_{28}F_4N_4O_4$ and a molecular weight of 572.55. The chemical name for letermovir is (4*S*)-2-{8-Fluoro-2-[4-(3- methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid. Letermovir is very slightly soluble in water.

The chemical structure of letermovir is:



14.2 Composition

PREVYMIS is available as 240 mg and 480 mg tablets.

PREVYMIS is also available as 240 mg and 480 mg concentrate for solution for infusion.

Active Ingredient
PREVYMIS tablets contain either 240 mg or 480 mg of letermovir.

PREVYMIS concentrate for solution for infusion is a clear, preservative-free sterile solution and may contain a few small translucent or white particles in single-dose vials of either 240 mg or 480 mg per vial. Each 1 mL of solution contains 20 mg letermovir.

Inactive Ingredients (List of excipients)
PREVYMIS tablets contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone 25, colloidal silicon dioxide, magnesium stearate and film-coated with a coating material containing the following inactive ingredients: lactose monohydrate, hypromellose 2910, titanium dioxide, triacetin, iron oxide yellow, and (only for 480 mg tablets) iron oxide red. Carnauba wax is added as a polishing agent.

Each 1 mL of PREVYMIS concentrate for solution for infusion contains the following inactive ingredients: hydroxypropyl betadex (150 mg), sodium chloride (3.1 mg), sodium hydroxide (1.2 mg), and Water for Injection. The amount of sodium hydroxide may be adjusted to achieve a pH of approximately 7.5.

14.3 Storage
Special Precautions for Storage
Store PREVYMIS tablets below 30° C.
Store PREVYMIS tablets in the original package until use.

Store PREVYMIS concentrate for solution for infusion vials below 30°C.
Store in the original carton to protect from exposure to light.

14.4 Incompatibilities
See 2 DOSAGE AND ADMINISTRATION, 2.10 Incompatible Diluents, Drug Products, and Other Materials Used for Intravenous Administration.

14.5 Shelf Life
Refer to outer carton.

14.6 Availability (a.k.a. Nature and Contents of Container)
PREVYMIS is supplied in pack size of 28 tablets.
PREVYMIS is supplied in pack size of 1 vial. Each single-use vial contains 20 mg/mL letermovir.

Product Owner:
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Date of revision: April 2023

MSD