HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREVYMIS safely and effectively. See full prescribing information for PREVYMIS.

PREVYMIS® (letermovir) tablets, for oral use
PREVYMIS® (letermovir) injection, for intravenous use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indications and Usage, CMV Prophylaxis in Kidney Transplant Recipients (1.2)	06/2023
Dosage and Administration, Recommended Dosage for Adult Patients (2.2)	08/2023

----------INDICATIONS AND USAGE----------

PREVYMIS is a CMV DNA terminase complex inhibitor indicated for:

- Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (1.1)
- Prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]). (1.2)

----------DOSAGE AND ADMINISTRATION----------

- HSCT: 480 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour through 100 days post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through 200 days post-HSCT. (2.1, 2.2)
- Kidney Transplant: 480 mg administered once daily orally or as an IV infusion over 1 hour through 200 days post-transplant. (2.1, 2.2)
- PREVYMIS injection must be administered through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter. (2.1, 2.7)
- Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation in HSCT recipients is recommended. (2.3)
- Dosage Adjustment: If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily. (2.4)
- Do not use PREVYMIS injection with IV bags and infusion set materials containing the plasticizer diethylhexyl phthalate (DEHP). (2.7, 2.9)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablet: 240 mg; 480 mg (3)
- Injection: 240 mg/12 mL (20 mg/mL) or 480 mg/24 mL (20 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------

PREVYMIS is contraindicated with:

- Pimozide. (4)
- Ergot Alkaloids. (4)
- Pitavastatin and simvastatin when co-administered with cyclosporine. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions: The concomitant use of PREVYMIS with certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug. Consult the full prescribing information for contraindications and dosage recommendations for concomitant drugs. (4, 5.1, 7.1, 7.2, 7.3)

---------- ADVERSE REACTIONS ----------

- HSCT Patients: Most common adverse events (occurring in at least 10% of subjects in the PREVYMIS group and at a frequency at least 2% greater than placebo) are nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, and abdominal pain. (6.1)
- Kidney Transplant Patients: Most common adverse event (occurring in at least 10% of subjects in the PREVYMIS group and at a frequency greater than valganciclovir) is diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch .

----------DRUG INTERACTIONS----------

- Dosage Adjustment: If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily. (2.4)
- Co-administration of PREVYMIS may alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PREVYMIS. Consult the full prescribing information prior to and during treatment for potential drug interactions. (2.4, 4, 5.1, 7.1, 7.2, 7.3, 7.4, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Renal Impairment: Closely monitor serum creatinine levels in patients with CLcr less than 50 mL/min using PREVYMIS injection. (8.6)
- Hepatic Impairment: PREVYMIS is not recommended for patients with severe (Child-Pugh C) hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 CMV Prophylaxis in Hematopoietic Stem Cell Transplant (HSCT) Recipients

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

1.2 CMV Prophylaxis in Kidney Transplant Recipients

PREVYMIS is indicated for prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]).

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing and Administration Information

PREVYMIS Tablets
- Administer with or without food.
- Swallow tablets whole.

PREVYMIS Injection
- 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 at a constant rate over 1 hour.
- Do not administer as an intravenous bolus injection.

2.2 Recommended Dosage for Adult Patients

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

Dosage of PREVYMIS should be adjusted when co-administered with cyclosporine *[see Dosage and Administration (2.4)]*.

PREVYMIS injection, which contains hydroxypropyl betadex, should be used only in patients unable to take oral therapy. Patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. PREVYMIS tablet and injection may be used interchangeably at the discretion of the physician, and no dosage adjustment is necessary when switching formulations.

HSCT
Initiate PREVYMIS between Day 0 and Day 28 post-HSCT (before or after engraftment) and continue through Day 100 post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through Day 200 post-HSCT *[see Clinical Studies (14.2)]*.

Kidney Transplant
Initiate PREVYMIS between Day 0 and Day 7 post-transplant and continue through Day 200 post-transplant.

2.3 Patient Monitoring

Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation in HSCT recipients is recommended *[see Clinical Studies (14.2)]*.

2.4 Dosage Adjustment When Co-administered with Cyclosporine

If oral or intravenous PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily *[see Drug Interactions (7.1, 7.2, 7.3) and Clinical Pharmacology (12.3)]*.

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

2.5 Use in Patients with Renal Impairment

- For patients with creatinine clearance (CLcr) greater than 10 mL/min, no dosage adjustment of PREVYMIS is required based on renal impairment *[see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.
- There are insufficient data in patients with CLcr 10 mL/min or less or in patients on dialysis to make PREVYMIS dosing recommendations.
- In patients with CLcr less than 50 mL/min receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, may occur. Closely monitor serum creatinine levels in these patients.

2.6 Use in Patients with Hepatic Impairment

No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment *[see Use in Specific Populations (8.7)]*.

2.7 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.

<u>Preparation and Administration Instructions</u>

- 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 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 the plasticizer diethylhexyl phthalate (DEHP). Use only with IV bags and infusion set materials that are DEHP-free. Materials that are phthalate-free are also DEHP-free.

- 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 for use 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:
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.

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

- 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).

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

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

- 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)]*.

2.8 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 (2.9)]*.

2.9 Incompatible Drug Products and Other Materials Used for Intravenous Administration

Incompatible Drug Products
PREVYMIS injection 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 DOSAGE FORMS AND STRENGTHS

Tablets

- PREVYMIS 240 mg tablet: yellow oval tablet with “591” on one side and corporate logo on the other side.
- PREVYMIS 480 mg tablet: pink oval, bi-convex tablet with “595” on one side and corporate logo on the other side.

Injection

- PREVYMIS 240 mg/12 mL (20 mg/mL) injection: clear solution in a single-dose vial.
- PREVYMIS 480 mg/24 mL (20 mg/mL) injection: clear solution in a single-dose vial.

4 CONTRAINDICATIONS

- PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids:
    - Pimozide: Concomitant administration of PREVYMIS in patients receiving pimozide may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, which may lead to QT prolongation and torsades de pointes *[see Warnings and Precautions (5.1) and Drug Interactions (7.2, 7.3)]*.
    - Ergot alkaloids: Concomitant administration of PREVYMIS in patients receiving ergot alkaloids may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism *[see Warnings and Precautions (5.1) and Drug Interactions (7.2, 7.3)]*.
- PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. 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 Warnings and Precautions (5.1) and Drug Interactions (7.2, 7.3)]*.

5 WARNINGS AND PRECAUTIONS

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

The concomitant use of PREVYMIS and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug *[see Contraindications (4) and Drug Interactions (7.1, 7.2, 7.3)]*.

See Table 4 for steps to prevent or manage these possible or known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during PREVYMIS therapy; review concomitant medications during PREVYMIS therapy; and monitor for adverse reactions associated with PREVYMIS and concomitant medications.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult CMV-seropositive Recipients [R+] of an Allogeneic HSCT
Prophylaxis Through Week 14 (~100 days) Post-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-HSCT. Adverse events were those reported while subjects were on study medication or within two weeks of study medication completion/discontinuation. The mean time for reporting adverse events and laboratory abnormalities was approximately 22% longer in the PREVYMIS arm compared to the placebo arm.

Cardiac Adverse Events
The cardiac adverse event rate 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.

Common Adverse Events
The rate of adverse events occurring in at least 10% of subjects in the PREVYMIS group and at a frequency at least 2% greater than placebo are outlined in Table 1.

Table 1: Trial P001 All Grade Adverse Events Reported in ≥ 10% of PREVYMIS-Treated HSCT Recipients at a Frequency at least 2% Greater than Placebo

Adverse Events	PREVYMIS (N=373)	Placebo (N=192)
nausea	27%	23%
diarrhea	26%	24%
vomiting	19%	14%
peripheral edema	14%	9%
cough	14%	10%
headache	14%	9%
fatigue	13%	11%

abdominal pain	12%	9%

Overall, similar proportions of subjects in each group discontinued study medication due to an adverse event (13% of PREVYMIS subjects vs. 12% of placebo subjects). The most frequently reported adverse event that led to study drug discontinuation was nausea, occurring in 2% of PREVYMIS subjects and 1% of placebo subjects. Hypersensitivity reaction, with associated moderate dyspnea, occurred in one subject following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

Laboratory Abnormalities

Selected laboratory abnormalities reported during treatment or within 2 weeks of stopping treatment are presented in the table below.

Table 2: Trial P001 Selected Laboratory Abnormalities

	PREVYMIS N=373	**Placebo N=192**
Absolute neutrophil count (cells/μL)		
< 500	19%	19%
500 – < 750	4%	7%
750 – < 1000	8%	9%
Hemoglobin (g/dL)		
< 6.5	2%	1%
6.5 – < 8.0	14%	15%
8.0 – < 9.5	41%	43%
Platelets (cells/μL)		
< 25000	27%	21%
25000 – < 50000	17%	18%
50000 – < 100000	20%	30%
Serum creatinine (mg/dL)		
> 2.5	2%	3%
> 1.5 – 2.5	17%	20%

The median time to engraftment (defined as absolute neutrophil count ≥ 500/mm^3 on 3 consecutive days after transplantation) was 19 days in the PREVYMIS group and 18 days in the placebo group.

Prophylaxis From Week 14 (~100 days) Through Week 28 (~200 days) Post-HSCT

The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, placebo-controlled trial (P040) in which 218 subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomized to treatment with PREVYMIS (N=144) or placebo (N=74) through Week 28 (~200 days) post-HSCT. Adverse events were those reported while subjects were on study drug or within two weeks of study drug completion/discontinuation.

The most commonly reported adverse events in P040 were similar to those reported in P001. Study drug was discontinued due to an adverse event in 5% of PREVYMIS subjects and 1% of placebo subjects. The cardiac adverse event rate was 4% in the PREVYMIS and placebo groups.

The rates of hematologic laboratory abnormalities were comparable in the PREVYMIS and placebo groups. Serum creatinine abnormalities > 1.5 mg/dL occurred in 15% of PREVYMIS and 8% of placebo subjects.

Adult Kidney Transplant Recipients [D+/R-]
The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, active comparator-controlled trial (P002) in which 589 subjects were treated with PREVYMIS (N=292) or valganciclovir (N=297) through Week 28 post-transplant. Adverse events were those reported while subjects were on study medication or within two weeks of study medication completion/discontinuation. In these subjects, diarrhea was reported in at least 10% of subjects in the PREVYMIS group and at a frequency greater than valganciclovir (PREVYMIS, 32%; valganciclovir, 29%). Study drug was discontinued due to an adverse event in 4% of PREVYMIS subjects and 14% of valganciclovir subjects. The most frequently reported adverse events that led to study drug discontinuation were neutropenia (PREVYMIS, 1%; valganciclovir, 2%) and leukopenia (PREVYMIS, 1%; valganciclovir, 5%).

Laboratory Abnormalities
Selected laboratory abnormalities reported through Week 28 post-transplant are presented in the table below.

Table 3: Trial P002 Selected Laboratory Abnormalities

	PREVYMIS N=292	**Valganciclovir N=297**
Absolute neutrophil count (cells/µL)		
< 500	2%	7%
500 – < 750	1%	4%
750 – < 1000	1%	8%
Total < 1000	5%	18%
Hemoglobin (g/dL)		
< 6.5	2%	0%
6.5 – < 8.0	4%	5%
8.0 – < 9.5	29%	32%
Total < 9.5	34%	37%
Platelets (cells/µL)		
< 50000	0%	0%
50000 – < 100000	1%	3%
Total < 100000	1%	3%
Leukocytes (cells/µL)		

< 1000	1%	2%
1000 – < 2000	5%	19%
2000 – < 2500	4%	14%
Total < 2500	10%	35%
Serum creatinine (mg/dL)		
> 2.5	24%	22%
> 1.5 – 2.5	49%	52%
Total > 1.5	73%	73%

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect 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 (Table 4).

Co-administration of PREVYMIS with 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 4)*.

7.2 Potential for PREVYMIS to Affect Other Drugs

Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentrations, indicating that letermovir is a moderate inhibitor of CYP3A *[see Clinical Pharmacology (12.3)]*. 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 (Table 4) *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

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 (Table 4).

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when PREVYMIS is co-administered with cyclosporine. See the prescribing information for cyclosporine for information on drug interactions with cyclosporine.

7.3 Established and Other Potentially Significant 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.

Table 4 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 Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

Table 4: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions* (Information in the

Table Applies to Co-administration of PREVYMIS and the Concomitant Drug without Cyclosporine, Unless Otherwise Indicated)

Concomitant Drug Class and/or Clearance Pathway: Drug Name	Effect on Concentration†	Clinical Comments
Anti-arrhythmic Agents		
amiodarone	↑ amiodarone	Close clinical monitoring for adverse events related to amiodarone is recommended during co-administration. Frequently monitor amiodarone concentrations when amiodarone is co-administered with PREVYMIS.
Antibiotics		
nafcillin	↓ letermovir	Co-administration of PREVYMIS and nafcillin is not recommended due to potential for loss of efficacy of PREVYMIS.
Anticoagulants		
warfarin	↓ warfarin	When PREVYMIS is co-administered with warfarin, frequently monitor International Normalized Ratio (INR)‡.
Anticonvulsants		
carbamazepine	↓ letermovir	Co-administration of PREVYMIS and carbamazepine is not recommended due to potential for loss of efficacy of PREVYMIS.
phenobarbital	↓ letermovir	Co-administration of PREVYMIS and phenobarbital is not recommended due to potential for loss of efficacy of PREVYMIS.
phenytoin	↓ letermovir ↓ phenytoin	Co-administration of PREVYMIS and phenytoin is not recommended due to potential for loss of efficacy of PREVYMIS.
Antidiabetic Agents		
Examples: glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ repaglinide ↑ rosiglitazone	When PREVYMIS is co-administered with glyburide, repaglinide, or rosiglitazone, frequently monitor glucose concentrations‡. When PREVYMIS is co-administered with cyclosporine, use of repaglinide is not recommended.
Antifungals		
voriconazole§	↓ voriconazole	If concomitant administration of voriconazole is necessary, closely monitor for reduced effectiveness of voriconazole‡.

Antimycobacterials		
rifabutin	↓ letermovir	Co-administration of PREVYMIS and rifabutin is not recommended due to potential for loss of efficacy of PREVYMIS.
rifampin§	↓ letermovir	Co-administration of PREVYMIS and rifampin is not recommended due to potential for loss of efficacy of PREVYMIS.
Antipsychotics		
pimozide	↑ pimozide	Co-administration is contraindicated due to risk of QT prolongation and torsades de pointes *[see Contraindications (4)]*.
thioridazine	↓ letermovir	Co-administration of PREVYMIS and thioridazine is not recommended due to potential for loss of efficacy of PREVYMIS.
Endothelin Antagonists		
bosentan	↓ letermovir	Co-administration of PREVYMIS and bosentan is not recommended due to potential for loss of efficacy of PREVYMIS.
Ergot Alkaloids		
ergotamine, dihydroergotamine	↑ ergotamine, dihydroergotamine	Co-administration is contraindicated due to risk of ergotism *[see Contraindications (4)]*.
Herbal Products		
St. John's wort (*Hypericum perforatum*)	↓ letermovir	Co-administration of PREVYMIS and St. John's wort is not recommended due to potential for loss of efficacy of PREVYMIS.
HIV Medications		
efavirenz	↓ letermovir	Co-administration of PREVYMIS and efavirenz is not recommended due to potential for loss of efficacy of PREVYMIS.
etravirine	↓ letermovir	Co-administration of PREVYMIS and etravirine is not recommended due to potential for loss of efficacy of PREVYMIS.
nevirapine	↓ letermovir	Co-administration of PREVYMIS and nevirapine is not recommended due to potential for loss of efficacy of PREVYMIS.
HMG-CoA Reductase Inhibitors		
atorvastatin§	↑ atorvastatin	When PREVYMIS is co-administered with atorvastatin, do not exceed an atorvastatin dosage

		of 20 mg daily‡. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of atorvastatin is not recommended.
pitavastatin, simvastatin	↑ HMG-CoA reductase inhibitors	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 due to significantly increased pitavastatin or simvastatin concentrations and risk of myopathy or rhabdomyolysis *[see Contraindications (4)]*.
fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	When PREVYMIS is co-administered with these statins, a statin dosage reduction may be necessary‡. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of lovastatin is not recommended. When PREVYMIS is co-administered with cyclosporine, refer to the statin prescribing information for specific statin dosing recommendations.
Immunosuppressants		
cyclosporine§	↑ cyclosporine ↑ letermovir	Decrease the dosage of PREVYMIS to 240 mg once daily *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. Frequently monitor cyclosporine whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of cyclosporine accordingly‡.
sirolimus§	↑ sirolimus	When PREVYMIS is co-administered with sirolimus, frequently monitor sirolimus whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of sirolimus accordingly§. When PREVYMIS is co-administered with cyclosporine and sirolimus, refer to the sirolimus prescribing information for specific sirolimus dosing recommendations‡.
tacrolimus§	↑ tacrolimus	Frequently monitor tacrolimus whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of tacrolimus accordingly‡.
Proton Pump Inhibitors		

omeprazole	↓ omeprazole	Clinical monitoring and dose adjustment may be needed.
pantoprazole	↓ pantoprazole	Clinical monitoring and dose adjustment may be needed.
Wakefulness-Promoting Agents		
modafinil	↓ letermovir	Co-administration of PREVYMIS and modafinil is not recommended due to potential for loss of efficacy of PREVYMIS.
CYP3A Substrates		
Examples: alfentanil, fentanyl, midazolam, and quinidine	↑ CYP3A substrate	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‡. 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‡. CYP3A substrates pimozide and ergot alkaloids are contraindicated *[see Contraindications (4)]*.

* This table is not all inclusive.
† ↓ =decrease, ↑ =increase
‡ Refer to the respective prescribing information.
§ These interactions have been studied *[see Clinical Pharmacology (12.3)]*.

7.4 Drugs without Clinically Significant Interactions with PREVYMIS

No clinically significant interactions were observed in clinical drug-drug interaction studies of letermovir and acyclovir, digoxin, mycophenolate mofetil, fluconazole, itraconazole, posaconazole, ethinyl estradiol, and levonorgestrel.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
No adequate human data are available to establish whether PREVYMIS poses a risk to pregnancy outcomes. In animal reproduction studies, embryo-fetal developmental toxicity (including fetal malformations) was observed in rats during the period of organogenesis at letermovir exposures (AUC) 11 times higher than human exposure at the recommended human dose (RHD). In rabbits, no embryo-fetal developmental toxicity was noted at exposures that were not maternally toxic (up to letermovir exposures 2 times higher than human exposure at the RHD). In a rat pre/post-natal development study, total litter loss was observed at maternal letermovir exposures approximately 2 times higher than human exposure at the RHD *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data

Letermovir was administered orally to pregnant rats at 0, 10, 50 or 250 mg/kg/day from gestation days 6 to 17. Developmental toxicities, including skeletal malformations and umbilical cord shortening, were observed at 250 mg/kg/day (approximately 11 times higher than human exposure at the RHD). In addition, decreased fetal body weight and skeletal variations (due to maternal toxicity) were observed at this dose. No embryo-fetal toxicities were observed at 50 mg/kg/day (approximately 3 times higher than human exposure 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. Developmental toxicities, including spontaneous abortion, increased post-implantation loss, and skeletal variations, were observed at a maternally toxic dose (225 mg/kg/day; approximately 2 times higher than human exposure at the RHD). No embryo-fetal toxicities were observed at 75 mg/kg/day (less than human exposure at the RHD).

In the pre/post-natal development 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. At 180 mg/kg/day (approximately 2 times higher than human exposure at the RHD), total litter loss due to stillbirth or possible maternal neglect was observed in 5 of 23 pregnant females by post-partum/lactation day 4. In surviving offspring, slight developmental delays in vaginal opening and pinna unfolding were accompanied by reduced body weight gain at this dose. No toxicities were observed at 45 mg/kg/day (similar to human exposure at the RHD).

8.2 Lactation

Risk Summary
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 the milk of lactating rats as well as the blood of nursing pups *(see Data)*.

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.

Data
In a lactation study, letermovir was excreted in milk when administered intravenously (at 10 mg/kg) to lactating rats on post-partum/lactation day 10. Letermovir was also detected in the blood of nursing pups on post-partum/lactation day 21 in the pre/post-natal developmental study.

8.3 Females and Males of Reproductive Potential

Infertility
There are no data on the effect of letermovir on human fertility. Decreased fertility due to testicular toxicity was observed in male rats *[see Nonclinical Toxicology (13.1, 13.2)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 373 subjects treated with PREVYMIS in Trial P001, 56 (15%) subjects were 65 years of age or older. Of 144 subjects treated with PREVYMIS in Trial P040, 32 (22%) subjects were 65 years of age or older. Of the 292 subjects treated with PREVYMIS in Trial P002, 48 (16%) subjects were 65 years of age or older. Safety and efficacy were similar across older and younger subjects in each trial. No dosage adjustment of PREVYMIS is required based on age *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

For patients with CLcr greater than 10 mL/min (by Cockcroft-Gault equation), no dosage adjustment of PREVYMIS is required based on renal impairment *[see Clinical Pharmacology (12.3)]*. The safety of PREVYMIS in patients with end-stage renal disease (CLcr less than 10 mL/min), including patients on dialysis, is unknown.

In patients with CLcr less than 50 mL/min receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, could occur. Closely monitor serum creatinine levels in these patients.

8.7 Hepatic Impairment

No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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 be instituted.

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

11 DESCRIPTION

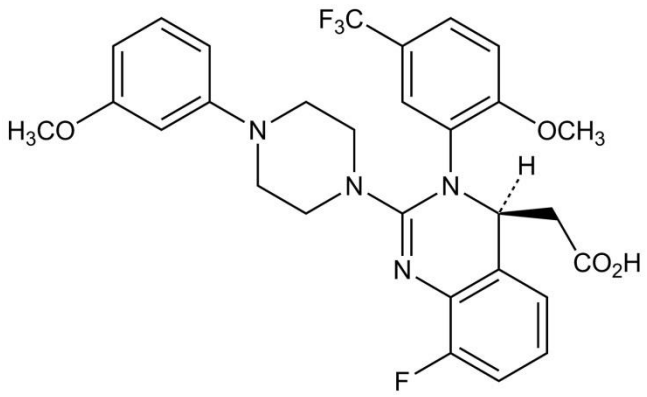
PREVYMIS contains letermovir, an inhibitor of the CMV DNA terminase complex, and is administered orally or by intravenous infusion.

PREVYMIS is available as 240 mg and 480 mg tablets. PREVYMIS tablets contain either 240 mg or 480 mg of letermovir and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone 25, and film-coated with a coating material containing the following inactive ingredients: hypromellose 2910, iron oxide red (only for 480 mg tablets), iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin. Carnauba wax is added as a polishing agent.

PREVYMIS is also available as 240 mg and 480 mg injection for intravenous infusion. PREVYMIS injection 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, hydroxypropyl betadex (150 mg), sodium chloride (3.1 mg), sodium hydroxide (1.2 mg), and Water for Injection, USP. The amount of sodium hydroxide may be adjusted to achieve a pH of approximately 7.5.

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:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PREVYMIS is an antiviral drug against CMV *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT trial in healthy subjects, letermovir at the therapeutic IV dose or at a dose of 2 times the approved IV dose did not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetic properties of letermovir are displayed in Table 5.

Table 5: Absorption, Distribution, Metabolism, Elimination (ADME), and Pharmacokinetic Properties of PREVYMIS*

Pharmacokinetics in HSCT Recipients	
Treatment Regimen	Steady-state median (90% prediction interval) AUC (ng•hr/mL) of PREVYMIS
480 mg oral once daily, no cyclosporine	34,400 (16,900, 73,700)
480 mg IV once daily, no cyclosporine	100,000 (65,300, 148,000)
240 mg oral once daily, with cyclosporine	60,800 (28,700, 122,000)
240 mg IV once daily, with cyclosporine	70,300 (46,200, 106,000)
Pharmacokinetics in Kidney Transplant Recipients	
Treatment Regimen	Steady-state median (90% prediction interval) AUC (ng•hr/mL) of PREVYMIS
480 mg oral once daily, no cyclosporine	62,700 (17,500, 139,000)
240 mg oral once daily, with cyclosporine	71,900 (42,400, 125,000)
Pharmacokinetics in Healthy Subjects	

Treatment Regimen 480 mg oral once daily	Steady-state geometric mean AUC and Cmax of PREVYMIS Cmax: 13,000 ng/mL AUC: 71,500 ng•hr/mL
Dose proportionality	Greater than proportional following single and multiple oral or IV doses of PREVYMIS 240 mg and 480 mg
Accumulation ratio†	Cmax: 1.03 AUC: 1.22
Time to steady-state	9-10 days
Absorption	
Bioavailability	Healthy subjects administered PREVYMIS without cyclosporine: 94% at an oral dose range of 240 mg to 480 mg HSCT recipients administered PREVYMIS without cyclosporine: 35% with 480 mg oral once daily HSCT recipients administered PREVYMIS with cyclosporine: 85% with 240 mg oral once daily Kidney transplant recipients administered PREVYMIS without cyclosporine: 56%‡ with 480 mg oral once daily
Median Tmax (hr)	1.5 to 3.0 hr
Effect of food (relative to fasting)§	AUC: 99.63% [84.27% - 117.80%] Cmax: 129.82% [104.35% -161.50%]
Distribution	
Mean steady-state volume of distribution	45.5 L following IV administration in HSCT recipients
% *In vitro* bound to human plasma proteins	99% across the concentration range of 0.2 to 50 mg/L
In vitro blood-to plasma ratio	0.56 across the concentration range of 0.1 to 10 mg/L
Metabolism	
In vitro metabolism	UGT1A1/1A3 (minor)
Drug-related component in plasma	97% unchanged parent No major metabolites detected in plasma
Elimination	
Route of elimination	Hepatic uptake (OATP1B1/3)

Mean terminal $t_{1/2}$ (hr)	12 hrs after dosing of PREVYMIS 480 mg IV once daily
% of dose excreted in feces¶	93%
% of dose excreted in urine¶	<2%
% of unchanged drug excreted in feces¶	70%

* Values were obtained in studies of healthy subjects unless otherwise indicated.

† Based on geometric mean data.

‡ 95% CI (46%, 65%)

§ Values refer to geometric mean ratio [fed/fasted] percentage and 90% confidence interval back transformed from linear mixed-effects model performed on natural log-transformed values. The meal administered was a standard high fat and high calorie meal (33 grams protein, 65 grams carbohydrates, 58 grams fat; 920 total calories).

¶ Single oral administration of radiolabeled letermovir in mass balance study.

Specific Populations

Pediatric Population

The pharmacokinetics of letermovir in patients less than 18 years of age have not been evaluated.

Age, Gender, Race, and Weight

Age (18 to 82 years), gender, race (White vs. non-White), and body weight (up to 100 kg) did not have a clinically significant effect on the pharmacokinetics of letermovir.

Renal Impairment

Clinical Study in a Renally Impaired Population

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/1.73m^2) and severe (eGFR less than 30 mL/min/1.73m^2) renal impairment, respectively, compared to healthy subjects.

Post-kidney Transplant

Based on population pharmacokinetic analysis, letermovir AUC was approximately 1.1-, 1.3- and 1.4-fold higher in subjects with mild (CLcr greater than or equal to 60 to less than 90 mL/min), moderate (CLcr greater than or equal to 30 to less than 60 mL/min) and severe (CLcr greater than or equal to 15 to less than 30 mL/min) renal impairment, respectively, compared to subjects with CLcr greater than or equal to 90 mL/min.

Intravenous Formulation

Hydroxypropyl betadex present in the intravenous letermovir formulation is mainly eliminated by glomerular filtration. Decreased elimination of hydroxypropyl betadex has been reported in the literature in patients with severe renal impairment.

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.

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 6 and Table 7)*.

In vitro results indicate that letermovir is a substrate of drug metabolizing enzymes CYP3A, CYP2D6, UGT1A1, and UGT1A3, and transporters OATP1B1/3 and P-gp. Oxidative metabolism is considered to be a minor elimination pathway based on *in vivo* human data. Inhibitors of OATP1B1/3 may result in increases in letermovir plasma concentrations. Changes in letermovir plasma concentrations due to inhibition of P-gp/BCRP by itraconazole were not clinically relevant. Changes in letermovir plasma concentrations due to inhibition of UGTs are not anticipated to be clinically relevant.

Based on *in vitro* studies, the metabolism of letermovir is not mediated by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2E1, CYP4A11, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, or UGT2B17. The transport of letermovir is not mediated by OATP2B1, OCT1, OAT1, BCRP, or MRP2 *in vitro*.

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 7)*. Based on these results, co-administration of PREVYMIS with CYP3A substrates may increase the plasma concentrations of the CYP3A substrates *[see Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7.2, 7.3), and Table 4]*. Letermovir is a reversible inhibitor of CYP2C8 *in vitro*. When co-administered with PREVYMIS, plasma concentrations of CYP2C8 substrates are predicted to be increased *[see Table 4 in Drug Interactions (7.3)].* 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 4 in Drug Interactions (7.3)]*. 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 4 in Drug Interactions (7.3)]*. 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 7)*. The effect of letermovir on BCRP, BSEP, and MRP2 substrates was not evaluated in clinical studies; the clinical relevance is unknown.

Based on *in vitro* results letermovir is not an inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 and is not an inducer of CYP1A2. Letermovir is not an inhibitor of OATP2B1, OCT1, OCT2, or OAT1 *in vitro*.

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

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	Geometric Mean Ratio [90% CI] of Letermovir PK with/without Co-administered Drug (No Effect=1.00)		
			AUC	Cmax	C24hr*
Antifungals					

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	Geometric Mean Ratio [90% CI] of Letermovir PK with/without Co-administered Drug (No Effect=1.00)		
			AUC	Cmax	C24hr*
fluconazole	400 mg single dose PO	480 mg single dose PO	1.11 (1.01, 1.23)	1.06 (0.93, 1.21)	1.28 (1.15, 1.43)
itraconazole	200 mg once daily PO	480 mg once daily PO	1.33 (1.17, 1.51)	1.21 (1.05, 1.39)	1.90 (1.58, 2.28)
Antimycobacterials					
rifampin	600 mg single dose PO	480 mg single dose PO	2.03 (1.84, 2.26)	1.59 (1.46, 1.74)	2.01 (1.59, 2.54)
	600 mg single dose IV	480 mg single dose PO	1.58 (1.38, 1.81)	1.37 (1.16, 1.61)	0.78 (0.65, 0.93)
	600 mg once daily PO	480 mg once daily PO	0.81 (0.67, 0.98)	1.01 (0.79, 1.28)	0.14 (0.11, 0.19)
	600 mg once daily PO (24 hours after rifampin)†	480 mg once daily PO	0.15 (0.13, 0.17)	0.27 (0.22, 0.31)	0.09 (0.06, 0.12)
Immunosuppressants					
cyclosporine	200 mg single dose PO	240 mg once daily PO	2.11 (1.97, 2.26)	1.48 (1.33, 1.65)	2.06 (1.81, 2.35)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	1.18 (1.04, 1.32)	1.11 (0.92, 1.34)	1.39 (1.12, 1.74)
tacrolimus	5 mg single dose PO	80 mg twice daily PO	1.02 (0.97, 1.07)	0.92 (0.84, 1.00)	1.02 (0.93, 1.12)

Abbreviations: PO= oral

* C12hr for tacrolimus

† These data are the effect of rifampin on letermovir 24 hours after final rifampin dose.

Table 7: Drug Interactions: Changes in Pharmacokinetics for Co-administered Drug in the Presence of Letermovir

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	Geometric Mean Ratio [90% CI] of Co-administered Drug PK with/without Letermovir (No Effect=1.00)		
			AUC	Cmax	C24hr*
CYP3A Substrates					
midazolam	1 mg single dose IV	240 mg once daily PO	1.47 (1.37, 1.58)	1.05 (0.94, 1.17)	2.74 (2.16, 3.49)
	2 mg single dose PO	240 mg once daily PO	2.25 (2.04, 2.48)	1.72 (1.55, 1.92)	Not available
P-gp Substrates					
digoxin	0.5 mg single dose PO	240 mg twice daily PO	0.88 (0.80, 0.96)	0.75 (0.63, 0.89)	0.90 (0.84, 0.96)
Immunosuppressants					
cyclosporine	50 mg single dose PO	240 mg once daily PO	1.66 (1.51, 1.82)	1.08 (0.97, 1.19)	2.19 (1.80, 2.66)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	1.08 (0.97, 1.20)	0.96 (0.82, 1.12)	1.04 (0.86, 1.27)
tacrolimus	5 mg single dose PO	480 mg once daily PO	2.42 (2.04, 2.88)	1.57 (1.32, 1.86)	2.53 (2.12, 3.03)
sirolimus	2 mg single dose PO	480 mg once daily PO	3.40 (3.01, 3.85)	2.76 (2.48, 3.06)	3.15 (2.80, 3.55)
Antifungals and Antivirals					
acyclovir	400 mg single dose PO	480 mg once daily PO	1.02 (0.87, 1.2)	0.82 (0.71, 0.93)	1.13 (0.94, 1.36)
fluconazole	400 mg single dose PO	480 mg single dose PO	1.03 (0.99, 1.08)	0.95 (0.92, 0.99)	1.04 (1.00, 1.08)
itraconazole	200 mg once daily PO	480 mg once daily PO	0.76 (0.71, 0.81)	0.84 (0.76, 0.92)	0.67 (0.61, 0.73)
posaconazole	300 mg single dose PO	480 mg once daily PO	0.98 (0.82, 1.17)	1.11 (0.95, 1.29)	1.10 (0.94, 1.30)
voriconazole	200 mg twice daily PO	480 mg once daily PO	0.56 (0.51, 0.62)	0.61 (0.53, 0.71)	0.49 (0.42, 0.57)
HMG-CoA Reductase Inhibitors					
atorvastatin	20 mg single dose PO	480 mg once daily PO	3.29 (2.84, 3.82)	2.17 (1.76, 2.67)	3.62 (2.87, 4.55)
Oral Contraceptives					
ethinyl estradiol (EE) /levonorgestrel (LNG)	0.03 mg EE single dose PO	480 mg once daily PO	1.42 (1.32, 1.52)	0.89 (0.83, 0.96)	1.57 (1.45, 1.70)
	0.15 mg LNG single dose PO		1.36 (1.30, 1.43)	0.95 (0.86, 1.04)	1.38 (1.32, 1.46)

Abbreviations: PO=oral

* C12hr reported for voriconazole.

12.4 Microbiology

Mechanism of Action

Letermovir inhibits the CMV DNA terminase complex (pUL51, pUL56, and pUL89) which is required for viral DNA processing and packaging. Biochemical characterization and electron microscopy demonstrated that letermovir affects the production of proper unit length genomes and interferes with virion maturation. Genotypic characterization of virus resistant to letermovir confirmed that letermovir targets the terminase complex.

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). There was no significant difference in EC_{50} value by CMV gB genotype (gB1=29; gB2=27; gB3=11; and gB4=3).

Combination Antiviral Activity

No antagonism of the antiviral activity was seen when letermovir was combined with CMV DNA polymerase inhibitors (cidofovir, foscarnet, or ganciclovir).

Viral Resistance

In Cell Culture

CMV mutants with reduced susceptibility to letermovir have been selected in cell culture and the resistance mutations map to UL51, UL56, and UL89. Resistance-associated substitutions were found in pUL51 (P91S, A95V), pUL56 (C25F, S229F, V231A/L, N232Y, V236A/L/M, E237D, L241P, T244K/R, L254F, L257F/I, K258E, F261C/L/S, Y321C, C325F/R/W/Y, L328V, M329T, A365S, N368D, R369G/M/S), 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 or placebo 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 on-treatment samples were available for analysis. One subject had a letermovir resistance substitution, pUL56 V236M (19-50-fold reduction in susceptibility).

In a Phase 3 trial (P001), DNA sequence analysis of the entire coding regions of UL56 and UL89 was performed on samples obtained from 50 letermovir-treated subjects who had received at least one dose of study drug and experienced prophylaxis failure and for whom samples were available for analysis. The pUL56 substitutions V236M (19-50-fold reduction), E237G (13-fold reduction), C325W (9300-fold reduction), and R369T (52-fold reduction) were detected in 3 subjects; however, no 2 subjects had substitutions at the same positions.

In a Phase 3 trial (P040), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 32 subjects (regardless of treatment group) who experienced prophylaxis failure or who discontinued early with CMV viremia. No letermovir resistance-associated substitutions were detected above the validated assay limit.

In a Phase 3 trial (P002), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 52 letermovir-treated subjects who experienced CMV disease or who discontinued early with CMV viremia. No previously characterized resistance-associated substitutions were identified. Novel substitutions were detected in letermovir-treated subjects at resistance-associated positions (pUL56 S229Y [n=1], pUL56 M329I [n=9], and pUL89 D344Y [n=5]) at low frequencies, ranging between 0.05 to 0.07. The clinical significance of these substitutions is unknown; phenotypic analysis is planned.

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 (cidofovir, foscarnet, and ganciclovir). These DNA polymerase inhibitors are expected to be fully active against viral populations with substitutions conferring resistance to letermovir.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis
Letermovir was not genotoxic in *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.

Letermovir was not carcinogenic in a 6-month RasH2 transgenic mouse study up to the highest doses tested (150 mg/kg/day in males and 300 mg/kg/day in females). Based on a comprehensive assessment of the available toxicology data and the CMV-specific target, letermovir is not expected to be carcinogenic in humans.

Impairment of Fertility
In a fertility and early embryonic development study in rats, no effects of letermovir on female fertility were observed at letermovir exposures (AUC) approximately 5 times higher than human exposure at the RHD.

In male rat fertility studies, decreased fertility associated with irreversible testicular toxicity was observed at ≥180 mg/kg/day (greater than or equal to 3 times the human exposure at the RHD). No fertility or testicular effects were observed at dose levels resulting in letermovir exposures (AUC) similar to human exposure at the RHD *[see Nonclinical Toxicology (13.2)]*.

13.2 Animal Toxicology and/or Pharmacology

Testicular toxicity in rats observed at ≥180 mg/kg/day (greater than or equal to 3 times the human exposure at the RHD) was characterized by decreased testis weight, bilateral seminiferous tubular degeneration, decreased sperm count and motility, and resultant decreased male fertility. Male reproductive system toxicities were not observed in either a monkey testicular toxicity study up to 240 mg/kg/day (approximately 2 times higher than human exposure at the RHD), or a general toxicology study in mice up to 250 mg/kg/day (approximately 3 times higher than human exposure at the RHD).

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

An overview of the trials contributing to the assessment of efficacy and safety of PREVYMIS in HSCT and kidney transplant recipients is provided in Table 8.

Table: 8 Trials Conducted with PREVYMIS

Trial (NCT Number)	**Population**	**Trial Arms (N)***	**Duration of Prophylaxis Post-Transplant**	**Primary Endpoint**
P001 (NCT02137772)	Adult allogeneic HSCT recipients [R+]	PREVYMIS (373) Placebo (192)	Through Week 14	Clinically significant CMV infection through Week 24 post-HSCT
P040 (NCT03930615)	Adult allogeneic HSCT recipients [R+] at risk for late CMV	PREVYMIS (144) Placebo (74)	Extension of prophylaxis from Week 14 through Week 28	Clinically significant CMV infection through

	infection and disease			Week 28 post-HSCT
P002 (NCT03443869)	Adult kidney transplant recipients [D+/R-]	PREVYMIS (292) Valganciclovir (297)	Through Week 28	CMV disease through Week 52 post-kidney transplant

* N represents the number of subjects treated.

14.2 Adult CMV-seropositive Recipients [R+] of an Allogeneic Hematopoietic Stem Cell Transplant (Trial P001 and Trial P040)

Prophylaxis Through Week 14 (~100 days) Post-HSCT (Trial P001)

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, NCT02137772) in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (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 (at any time from Day 0 to Day 28 post-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or intravenously; the dose of PREVYMIS was the same regardless of the route of administration. Subjects received CMV DNA monitoring weekly until post-HSCT Week 14 and then bi-weekly until post-HSCT Week 24, with initiation of standard-of-care CMV pre-emptive therapy if CMV viremia was considered clinically significant. Subjects had continued follow-up through Week 48 post-HSCT.

Among the 565 treated subjects, 70 subjects were found to have CMV viremia prior to study drug initiation and were therefore excluded from the efficacy analyses. The efficacy population consisted of 325 subjects who received PREVYMIS (including 91 subjects who received at least one IV dose) and 170 who received placebo (including 41 subjects who received at least one IV dose). The IV formulation of PREVYMIS was used at investigators' discretion in subjects who were unable to take oral therapy (e.g., unable to tolerate oral intake). The median time to starting study drug was 8 days after transplantation. Thirty-four percent (34%) of subjects were engrafted at baseline. The median age was 55 years (range: 18 to 76 years). 57% were male; 84% were White; 9% were Asian; 2% were Black or African American; and 5% were other (American Indian or Alaska Native, multiple, and missing). 7% were Hispanic or Latino; 89% not Hispanic or Latino; and 4% other (not reported, unknown, and missing).

At baseline, 30% of all subjects had one or more of the following factors associated with increased risk for CMV reactivation (high risk stratum): Human Leukocyte Antigen (HLA)-related 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 70% of subjects did not meet any of these high risk stratum criteria and were therefore included in the low risk stratum. Additionally, 48% of subjects received a myeloablative regimen, 51% were receiving cyclosporine, and 43% were receiving tacrolimus. The most common primary reasons for transplant were acute myeloid leukemia (38%), myelodysplastic syndrome (16%), and lymphoma (12%).

Clinically Significant CMV Infection

The primary efficacy endpoint of Trial P001 was the incidence of clinically significant CMV infection through Week 24 post-HSCT (prophylaxis failure). 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 protocol-specified guidance for CMV DNA thresholds for the initiation of PET during the treatment period was ≥ 150 copies/mL or > 300 copies/mL for subjects in the high and low risk strata, respectively. From Week 14 through Week 24, the threshold was >300 copies/mL for both high and low risk strata subjects. The Non-

Completer=Failure (NC=F) approach was used, where subjects who discontinued from the trial prior to Week 24 post-HSCT or had a missing outcome at Week 24 post-HSCT were counted as failures.

Efficacy results from Trial P001 are shown in Table 9.

Table 9: Trial P001 Incidence of Clinically Significant CMV Infection in HSCT Recipients (NC=F Approach, FAS Population) Through Week 24

Parameter	PREVYMIS (N=325)	Placebo (N=170)
Proportion of subjects who failed prophylaxis	**38%**	**61%**
Reasons for failures*		
Clinically significant CMV infection by Week 24†	18%	42%
Initiation of PET based on documented CMV viremia	16%	40%
CMV end-organ disease	2%	2%
Discontinued from study before Week 24‡	17%	16%
Missing outcome in Week 24 visit window	3%	3%
Stratum-adjusted treatment difference (PREVYMIS-Placebo)§		
Difference (95% CI)	-23.5 (-32.5, -14.6)¶	

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

† Through Week 14, 8% of subjects in the PREVYMIS group and 39% of subjects in the placebo group experienced clinically significant CMV infection.

‡ Reasons for discontinuation included adverse event, death, lost to follow-up, physician decision, and withdrawal by subject.

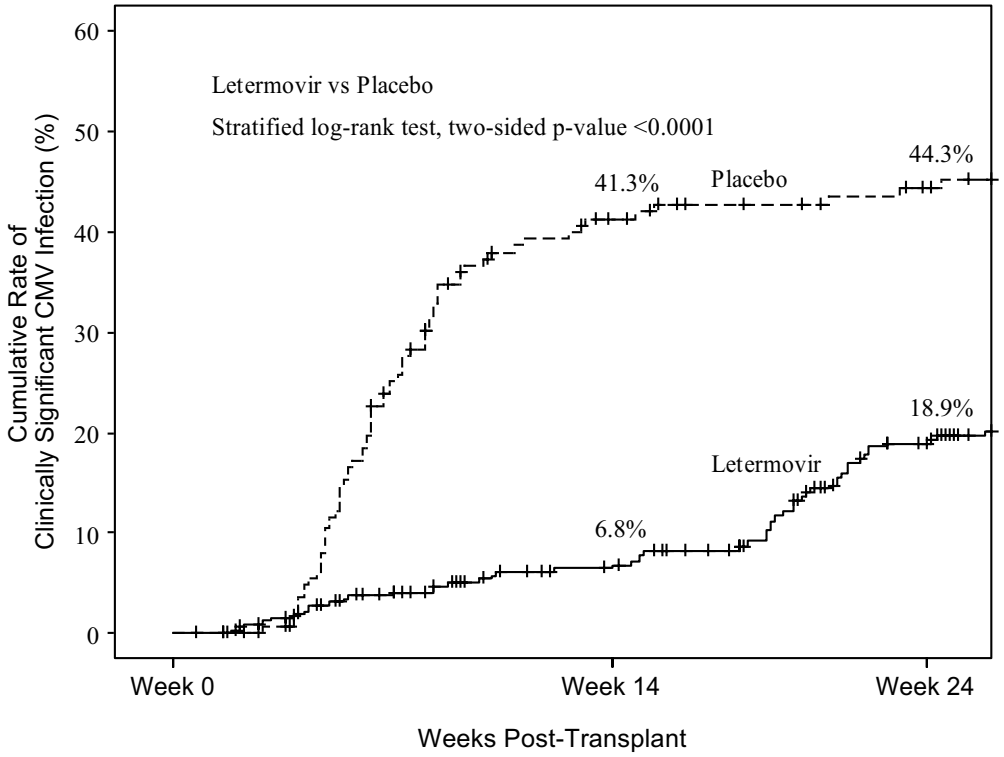
§ 95% CI and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

¶ p-value <0.0001.

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-HSCT visit window.

Efficacy results were consistent across high and low risk strata for CMV reactivation. The time to clinically significant CMV infection is shown in Figure 1. Among subjects in the PREVYMIS group, the cumulative rate of clinically significant CMV infection increased from 6.8% at the end of prophylaxis (Week 14) to 18.9% at Week 24. In the placebo group, the cumulative rate of clinically significant CMV infection increased from 41.3% at Week 14 to 44.3% at Week 24 *[see Dosage and Administration (2.3)].*

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

Post-hoc analysis demonstrated that among PREVYMIS-treated subjects, inclusion in the high risk stratum for CMV reactivation at baseline, occurrence of GVHD, and steroid use at any time after randomization may be associated with the development of clinically significant CMV infection between Week 14 and Week 24 post-HSCT.

Mortality
The Kaplan-Meier event rate for all-cause mortality in the PREVYMIS vs. placebo groups was 12% vs. 17% at Week 24 post-HSCT, and 24% vs. 28% at Week 48 post-HSCT.

Prophylaxis From Week 14 (~100 days) Through Week 28 (~200 days) Post-HSCT (Trial P040)
The efficacy of extending PREVYMIS prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT in patients at risk for late CMV infection and disease was assessed in a multicenter, double-blind, placebo-controlled Phase 3 trial (P040, NCT03930615) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Eligible subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomized (2:1) to receive PREVYMIS or placebo from Week 14 through Week 28 post-HSCT. Subjects received PREVYMIS at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with cyclosporine) or placebo. Study drug was administered either orally or IV; the dose of

PREVYMIS was the same regardless of the route of administration. One subject received IV PREVYMIS for 2 days. Subjects were monitored through Week 28 post-HSCT for the primary efficacy endpoint with continued off-treatment follow-up through Week 48 post-HSCT.

Among the 218 treated subjects, 144 subjects received PREVYMIS and 74 received placebo. The median age was 55 years (range: 20 to 74 years); 62% were male; 79% were white; 11% were Asian; 2% were Black; 1% were multiple races; 6% had missing race; and 10% were Hispanic or Latino.

At study entry, all subjects had risk factors for late CMV infection and disease, with 64% having two or more risk factors. The risk factors included: 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; receipt of anti-thymocyte globulin; receipt of alemtuzumab; use of systemic prednisone (or equivalent) at a dose of ≥1 mg/kg of body weight per day. The most common reasons for transplant were acute myeloid leukemia (42%), acute lymphocytic leukemia (15%), and myelodysplastic syndrome (11%).

Clinically Significant CMV Infection
The primary efficacy endpoint of Trial P040 was the incidence of clinically significant CMV infection through Week 28 post-HSCT. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the subject. The Observed Failure (OF) approach was used, where subjects who discontinued prematurely from the study without viremia or were missing data at the timepoint were not counted as failures. The number of subjects who discontinued from the study before Week 28 without viremia was 14 (9.7%) in the PREVYMIS arm and 0 in the placebo arm. The number of subjects with a missing outcome in the Week 28 visit window was 3 (2.1%) in the PREVYMIS arm and 4 (5.4%) in the placebo arm, none had prior viremia.

Efficacy results from Trial P040 are shown in Table 10. Efficacy was consistent across subgroups based on participant characteristics (age, gender, race) and risk factors for late CMV infection and disease.

Table 10: Trial P040 Efficacy Results in HSCT Recipients at Risk for Late CMV Infection and Disease (OF Approach, FAS Population)

Parameter	PREVYMIS (~200 days PREVYMIS) (N=144)	Placebo (~100 days PREVYMIS) (N=74)
Failures*	**2.8%**	**18.9%**
Clinically significant CMV infection from Week 14 through Week 28†	1.4%	17.6%
Initiation of PET based on documented CMV viremia	0.7%	14.9%
CMV end-organ disease	0.7%	2.7%
Discontinued from study with CMV viremia before Week 28	1.4%	1.4%
Stratum-adjusted treatment difference (PREVYMIS (~200 days PREVYMIS)-Placebo (~100 days PREVYMIS))‡		
Difference (95% CI)	-16.1 (-25.8, -6.5)§	

* 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 (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the subject.

‡ The 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 (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for declaring statistical significance.

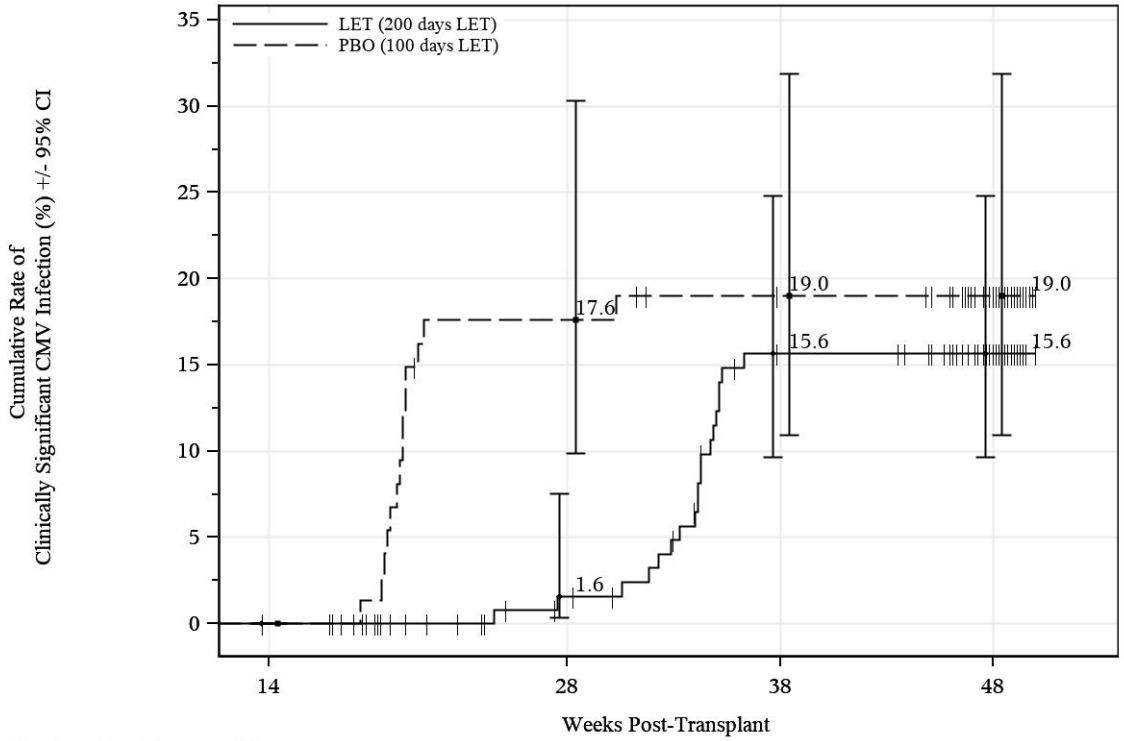
§ p-value = 0.0005

Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all subjects who developed clinically significant CMV infection or discontinued prematurely from the study with CMV viremia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.

N = Number of subjects in each treatment group.

The time to clinically significant CMV infection is shown in Figure 2. Among subjects in the PREVYMIS group, the cumulative rate of clinically significant CMV infection increased from 1.6% at the end of prophylaxis (Week 28) to 15.6% at Week 38. In the placebo group, the cumulative rate of clinically significant CMV infection increased from 17.6% at Week 28 to 19.0% at Week 38. There were no additional cases of clinically significant CMV infection in either group between Weeks 38 and 48 *[see Dosage and Administration (2.3)]*.

Figure 2: Trial P040 Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection From Week 14 Through Week 48 Post-transplant in HSCT Recipients at Risk for Late CMV Infection and Disease (FAS Population)



Number of subjects at risk

LET (200 days LET)	143	123	99	74
PBO (100 days LET)	74	60	55	38

LET = Letermovir; PBO = Placebo

14.3 Adult CMV-seronegative Recipients of a Kidney Transplant from a CMV-seropositive Donor [D+/R-] (Trial P002)

To evaluate PREVYMIS prophylaxis as a preventive strategy for CMV disease in kidney transplant recipients, the efficacy of PREVYMIS was assessed in a multicenter, double-blind, active comparator-controlled non-inferiority Phase 3 trial (P002, NCT03443869) in adult kidney transplant recipients at high risk [D+/R-]. Subjects were randomized (1:1) to receive either PREVYMIS or valganciclovir. PREVYMIS was administered at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with cyclosporine). PREVYMIS was given concomitantly with acyclovir. Valganciclovir was given concomitantly with a placebo to acyclovir. Randomization was stratified by the use or nonuse of highly cytolytic, anti-lymphocyte immunotherapy during induction. Study drug was initiated between Day 0 and Day 7 post-kidney transplant and continued through Week 28 (~200 days) post-transplant. Study drug was administered either orally or IV; the dose of PREVYMIS was the same regardless of the route of administration. Three subjects received IV PREVYMIS for a mean duration of 1.7 days. Subjects were monitored through Week 52 post-transplant.

Among the 589 treated subjects, 292 subjects received PREVYMIS and 297 received valganciclovir. The median age was 51 years (range: 18 to 82 years); 72% were male; 84% were White; 9% were Black; 3% were multiple; 2% were Asian; 1% Alaskan native or American Indian; 17% were Hispanic or Latino; and 60% received a kidney from a deceased donor. The most common primary reasons for transplant were congenital cystic kidney disease (17%), hypertension (16%), and diabetes/diabetic nephropathy (14%).

CMV Disease
The primary efficacy endpoint of Trial P002 was the incidence of CMV disease (CMV end-organ disease or CMV syndrome, confirmed by an independent adjudication committee) through Week 52 post-transplant. The Observed Failure (OF) approach was used, where subjects who discontinued prematurely from the study for any reason or were missing data at the timepoint were not counted as failures. The number of subjects who discontinued from the study before Week 52 was 32 (11%) in the PREVYMIS arm and 28 (9%) in the valganciclovir arm. The number of subjects with a missing outcome in the Week 52 visit window was 24 (8%) in the PREVYMIS arm and 25 (8%) in the valganciclovir arm.

Efficacy results from Trial P002 are shown in Table 11.

Table 11: Trial P002 Incidence of CMV Disease in Kidney Transplant Recipients (OF Approach, FAS Population) Through Week 52

Parameter	PREVYMIS (N=289)	Valganciclovir (N=297)
CMV Disease[*] Through Week 52	**10%**	**12%**
CMV Syndrome[†]	8%	11%
CMV End-organ Disease	2%	<1%
Stratum-adjusted Treatment Difference[‡] (PREVYMIS – Valganciclovir)	-1.4 (-6.5, 3.8)[§]	

* CMV disease cases confirmed by an independent adjudication committee.

† Defined as evidence of CMV in blood by viral isolation, rapid culture, antigenemia, or nucleic acid testing, and two or more of the following: 1) fever ≥38°C for at least 2 days, 2) new or increased malaise/fatigue, 3) leukopenia or neutropenia on two separate measurements at least 24 hours apart, 4) ≥5% atypical lymphocytes, 5) thrombocytopenia, 6) elevation of ALT or AST to 2x ULN.

‡ The 95% CIs 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 (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

§ Based on a non-inferiority margin of 10%, PREVYMIS is non-inferior to valganciclovir.

Note: Approach to handling missing values: Observed failure (OF) approach. With OF approach, subjects who discontinued from the study before Week 52 or had a missing outcome in the Week 52 visit window were not counted as failures.

Efficacy was comparable across all subgroups, including the use/nonuse of highly cytolytic, anti-lymphocyte immunotherapy during induction.

In an exploratory analysis of the incidence of CMV disease through Week 28 post-transplant, the difference (PREVYMIS – Valganciclovir) was -1.7% with 95% CI of (-3.4, 0.1). No subjects in the PREVYMIS group experienced CMV disease through Week 28 post-transplant (end of treatment period) compared with 5 subjects in the valganciclovir group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets:

Each 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. Each PREVYMIS 480 mg tablet is a pink oval, bi-convex tablet debossed with “595” on one side and corporate logo on the other side.
The 240 mg tablets are packaged into a carton (NDC 0006-3075-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 28 tablets, or into a carton (NDC 0006-3075-04) containing two (2) unit-dose 7-count blister cards for a total of 14 tablets.

The 480 mg tablets are packaged into a carton (NDC 0006-3076-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 28 tablets, or into a carton (NDC 0006-3076-04) containing two (2) unit-dose 7-count blister cards for a total of 14 tablets.

Store PREVYMIS tablets in the original package until use.

Store PREVYMIS tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Injection:

PREVYMIS is supplied as a sterile, clear solution for intravenous use of 240 mg (12 mL per vial) or 480 mg (24 mL per vial) that may contain a few product-related small translucent or white particles. The final solutions for infusion are obtained by dilution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

The single dose vials are supplied in cartons that contain a 240 mg single-dose vial (NDC 0006-5003-01) or a 480 mg single-dose vial (NDC 0006-5004-01).

Store PREVYMIS injection vials at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store in the original carton to protect from exposure to light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions
Inform patients that PREVYMIS may interact with some drugs; therefore, advise patients to report the use of any prescription, non-prescription medication, or herbal products to their healthcare provider *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]*.

Administration
Inform patients that it is important not to miss or skip doses and to take PREVYMIS for the duration that is recommended by the healthcare provider. 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.

Storage
Advise patients to store PREVYMIS tablets in the original package until use *[see How Supplied/Storage and Handling (16)]*.

Distributed by: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

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