Report on the Deliberation Results

March 8, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg
Non-proprietary Name	Letermovir (JAN*)
Applicant	MSD K.K.
Date of Application	July 28, 2017

Results of Deliberation

In its meeting held on March 2, 2018, the Second Committee on New Drugs concluded that the products may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The products are not classified as a biological product or a specified biological product, and the re-examination period is 10 years. The drug products and their drug substance are both classified as powerful drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

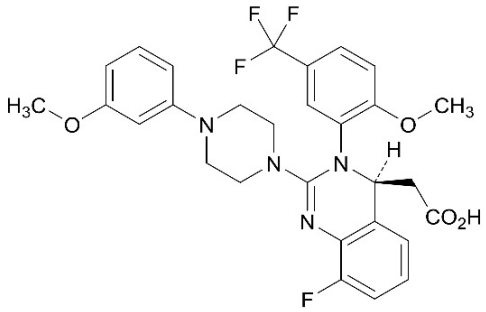
Review Report

February 8, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical products submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Prevymis Tablets 240 mg (b) Prevymis Intravenous Infusion 240 mg
Non-proprietary Name	Letermovir
Applicant	MSD K.K.
Date of Application	July 28, 2017
Dosage Form/Strength	(a) Tablet: Each film-coated tablet contains 240 mg of letermovir. (b) Injection: An aqueous solution contains 240 mg of letermovir in a vial (12 mL).
Application Classification	(a) and (b) Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{29}H_{28}F_4N_4O_4$
Molecular weight: 572.55
Chemical name:
(4S)-2-{8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid

Items Warranting Special Mention
Orphan drug (Drug Designation No. 374 of 2016 [28 yaku]; PSEHB/ELD Notification No. 0225-1 dated February 25, 2016, by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that Prevymis Tablets 240 mg and Prevymis Intravenous Infusion 240 mg have efficacy in the prophylaxis of cytomegalovirus disease, and that Prevymis Tablets 240 mg and Prevymis Intravenous Infusion 240 mg have acceptable safety in view of their benefits (see Attachment).

As a result of its review, PMDA has concluded that the products may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

(a) and (b)

Prophylaxis of cytomegalovirus disease in allogeneic hematopoietic stem cell transplant recipients

Dosage and Administration

(a) The usual adult dosage is 480 mg of letermovir administered orally once daily. If Prevymis is co-administered with cyclosporine, the dosage should be 240 mg of letermovir administered orally once daily.

(b) The usual adult dosage is 480 mg of letermovir administered by intravenous infusion over approximately 60 minutes once daily. If Prevymis is co-administered with cyclosporine, the dosage should be 240 mg of letermovir administered by intravenous infusion over approximately 60 minutes once daily.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

December 22, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Products Submitted for Approval

Brand Name	(a) Prevymis Tablets 240 mg
	(b) Prevymis Intravenous Infusion 240 mg
Non-proprietary Name	Letermovir
Applicant	MSD K.K.
Date of Application	July 28, 2017

Dosage Form/Strength

(a) Tablet: Each film-coated tablet contains 240 mg of letermovir.

(b) Injection: An aqueous solution contains 240 mg of letermovir in a vial (12 mL).

Proposed Indication

Prevention of cytomegalovirus infection or cytomegalovirus disease in allogeneic hematopoietic stem cell transplant recipients

Proposed Dosage and Administration

(a) The usual adult dosage is 480 mg of letermovir administered orally once daily. If Prevymis is co-administered with cyclosporine, the dosage should be decreased to 240 mg of letermovir once daily.

(b) The usual adult dosage is 480 mg of letermovir administered by intravenous infusion over approximately 60 minutes once daily. If Prevymis is co-administered with cyclosporine, the dosage should be decreased to 240 mg of letermovir once daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Human cytomegalovirus (CMV) is a member of the β-herpesvirus subfamily. CMV infection is generally acquired during infancy through secreted material such as saliva of CMV carriers (mostly latent infection), and then the virus remains latent in the body for life. Although the CMV seroprevalence in the Japanese adult population was reported to be 80% to 90%, a trend towards decreasing seroprevalence has been reported recently (Guideline of Japan Society for Hematopoietic Cell Transplantation, Volume 1, *Medicine and Drug Journal*. 2014;126-61, *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2010;46:1273-9, *Obstetrical and Gynecological Therapy*. 2008;97:485-93). CMV is known to be reactivated in latently infected individuals due to immunosuppression, inflammation, infection, stress, etc. Especially, allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients are immunocompromised and at risk for developing CMV disease due to CMV reactivation etc. Since CMV disease may lead to a deteriorated general condition or death in allo-HSCT recipients, it is a serious complication. The Japanese clinical practice guideline recommends preventive measures against CMV disease for allo-HSCT recipients (Guideline of Japan Society for Hematopoietic Cell Transplantation, Volume 1, *Medicine and Drug Journal*. 2014;126-61). This clinical practice guideline lists prophylactic therapy and preemptive therapy for the prevention of CMV disease after allo-HSCT. In Japan, there are no drugs approved for the prophylaxis of CMV disease in allo-HSCT recipients, and preemptive therapy (initiation of treatment with anti-CMV agents after detection of CMV viremia, etc. [e.g., a positive test result for CMV antigenemia]) is mainly used at medical institutions. On the other hand, it has been reported that CMV reactivation is associated with an increased risk of overall mortality in the first year after hemopoietic stem cell transplantation, independent of the use of preemptive therapy, and with higher viral loads associated with higher risk of death (*Lancet Haematol*. 2016;3:e119-27). The currently approved anti-CMV agents, which are used for preemptive therapy, are also associated with myelotoxicity, nephrotoxicity, etc. Thus, there is an unmet medical need for an effective and well-tolerated antiviral agent for the prevention of CMV disease in allo-HSCT recipients.

Letermovir is considered to prevent viral replication by inhibiting the UL56 subunit of the CMV terminase complex. The viral terminase complex cleaves viral progeny DNA into unit-length genomes that will be individually packaged into empty viral capsids. Letermovir was discovered by AiCuris GmbH & Co. KG and Bayer Healthcare AG. Merck Sharp & Dohme Corp. (the US), a subsidiary of Merck & Co., Inc., acquired the rights for the development of letermovir, and conducted a global phase III study in allo-HSCT recipients, involving Japan (Study 001), etc. Based on the results from clinical studies in allo-HSCT recipients, etc., the applicant has now filed marketing applications for Prevymis Tablets 240 mg and Prevymis Intravenous Infusion 240 mg.

Outside Japan, letermovir has been approved in the US and Canada, and EU application etc. are under review, as of November 2017.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder, and the general properties of the drug substance, including thermal analysis, solubility, optical rotation, crystalline polymorphism, hygroscopicity, partition coefficient, pH, and dissociation constant, have been determined.

The drug substance has 1 chiral center, and its chemical structure has been elucidated by ultraviolet-visible spectrophotometry, infrared spectrophotometry, nuclear magnetic resonance spectroscopy (^{1}H- and ^{13}C-NMR), mass spectrometry, and single crystal x-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], [redacted], and [redacted] as starting materials.

Based on the following studies etc., a quality control strategy was developed.

- Identification of [redacted] ([redacted] and [redacted]), [redacted], [redacted], [redacted], and [redacted] as critical quality attributes (CQAs).
- Identification of critical process parameters (CPPs) through quality risk assessment
- Establishment of the specifications and control methods for raw materials, starting materials, and intermediate products, and identification of process control items.
- Establishment of the specifications and control methods for the drug substance.

[redacted] synthesis with [redacted] has been defined as a critical step. [redacted], [redacted], and [redacted] have been defined as critical intermediates, and control items and values have been established for each of these critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (infrared spectrophotometry), purity (related substances [HPLC], chiral purity [HPLC], residual solvents [gas chromatography]), water content, residue on ignition, bacterial endotoxins, microbial limits, and assay (HPLC). Bacterial endotoxins and microbial limits are applied to batches used to manufacture the injection.

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 1. The photostability testing of the exposed samples showed that the drug substance is photosensitive.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	Double low-density polyethylene bags (with [redacted]) + high-density polyethylene drum	24 months
Accelerated	3 commercial-scale batches	40°C	75%RH		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when packaged in double low-density polyethylene bags with [redacted] within a high-density polyethylene drum and stored at room temperature, protected from light. The re-test period was determined in accordance with the Guideline on Evaluation of Stability Data (PFSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing will be continued up to [redacted] months.

2.2 Drug product (Prevymis Tablets 240 mg)

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet containing 240 mg of letermovir. The excipients used are microcrystalline cellulose, croscarmellose sodium, povidone, colloidal silicon dioxide, magnesium stearate, Opadry II Yellow ([redacted]), and carnauba wax.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of blending, lubrication and blending, [redacted], [redacted], lubrication and blending, tableting, coating, polishing, packaging, labeling, testing, and storage. Among these process steps, [redacted] has been defined as a critical step, and process control items and values have been established for each of [redacted] and packaging.

Based on the following studies etc., a quality control strategy was developed.

- Identification of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as CQAs.
- Identification of CPPs through quality risk assessment, formulation development based on the target product profile, and multi-factor and single-factor experiments.
- Development of design space for [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (HPLC), purity (related substances [HPLC]), uniformity of dosage units (mass variation test), microbial limits, dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 2. The photostability data showed that the drug product is photostable.

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	30°C	75%RH	PTP (aluminum-aluminum blisters)	24 months
Accelerated	3 commercial-scale batches	40°C	75%RH		6 months

Based on the above, a shelf-life of 36 months has been proposed for the drug product when packaged in PTP (aluminum-aluminum blisters) and stored at room temperature. The shelf-life was determined in accordance with the Guideline on Evaluation of Stability Data (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The applicant explained that the long-term testing will be continued up to [redacted] months.

2.3 Drug product (Prevymis Intravenous Infusion 240 mg)

2.3.1 Description and composition of drug product and formulation development

The drug product is an aqueous solution containing 240 mg of letermovir in a vial for intravenous infusion. The excipients used are hydroxypropyl-β-cyclodextrin (HP-β-CD), sodium chloride, sodium hydroxide, and water for injection.

2.3.2 Manufacturing process

The drug product is manufactured through a process comprised of drug solution preparation, bioburden reduction and filtration, [redacted], [redacted], packaging, labeling, testing, and storage. Among these process steps, [redacted], [redacted], [redacted], and [redacted] have been defined as critical steps, and process control items and values have been established for each of these critical steps.

Based on the following studies etc., a quality control strategy was developed.

- Identification of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as CQAs.
- Determination of the target product profile.
- Identification of CPPs through quality risk assessment.

2.3.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (HPLC), pH, purity (related substances [HPLC]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, and assay (HPLC).

2.3.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 3. The photostability data showed that the drug product is photosensitive.

Table 3. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	glass vial + chlorobutyl rubber stopper + aluminium cap	24 months
Accelerated	3 commercial-scale batches	40°C	75%RH		6 months

Based on the above, a shelf-life of 36 months has been proposed for the drug product when filled into a glass vial sealed tightly with a chlorobutyl rubber stopper and an aluminium cap and stored at room temperature, protected from light. The shelf-life was determined in accordance with the Guideline on Evaluation of Stability Data (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The applicant explained that the long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations etc., PMDA concluded that the quality of the drug substance and each drug product is adequately controlled.

2.R.1 Novel excipients

An aqueous solution for intravenous infusion, "Prevymis Intravenous Infusion 240 mg" contains HP-β-CD as an excipient. HP-β-CD appears in the list of excipients that are allowed to be used only in specific formulations or under specific conditions, in relation to "Handling of excipients that are allowed to be used only in specific formulations or under specific conditions" (MHLW/PFSB/ELD Administrative Notice dated June 23, 2009).[1)]

2.R.1.1 Specification and stability

HP-β-CD conforms to the United States Pharmacopeia and the European Pharmacopoeia. PMDA confirmed that the submitted HP-β-CD specification is appropriate.

The applicant's explanation about the stability of HP-β-CD:

The applicant obtained the following information: In the stability testing conducted by [redacted], the manufacturer of HP-β-CD, HP-β-CD was stable for [redacted] months when stored in double polyethylene bags within a high-density polyethylene container under the conditions of [redacted] and [redacted].[2)] This stability testing was conducted in accordance with International Pharmaceutical Excipients Council (IPEC)'s guideline on the stability of excipients, IPEC Excipient Stability Program Guide 2010 (http://ipec-europe.org/UPLOADS/100311_IPECStabilityGuide-Final.pdf [checked in December 2017]). In the stability testing conducted by the applicant ([redacted] batch only), HP-β-CD was stable for [redacted] months when stored in double polyethylene bags within a high-density polyethylene container under the conditions of [redacted] and [redacted]. Based on the above, HP-β-CD should be stable for at least [redacted] months.

PMDA's view:

Taking into account that the stability of HP-β-CD was demonstrated under the controlled testing conditions such as [redacted], the applicant's explanation (HP-β-CD is stable for [redacted] months) is acceptable.

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1) Present as a solubilizer in the IV formulation of letermovir. For selection of a solubilizer, [redacted] were assessed. Since solubilizers other than HP-β-CD were [redacted] etc., HP-β-CD was selected.

2) The manufacturer of HP-β-CD did not disclose specific testing conditions (temperature, humidity, light exposure condition, etc.) or test results to the applicant. The manufacturer of HP-β-CD submitted a statement that HP-β-CD was stable for [redacted] months, to the applicant.

2.R.1.2 Safety

HP-β-CD is present as an excipient in an approved product Itrizole Injection 1%. During the review of this product, however, it was concluded that HP-β-CD should be handled as a novel excipient for use in other products because the excipient has a very narrow safety margin for effects on the kidney or liver (Itrizole Injection 1% Review Report as of August 10, 2006).

In repeated intravenous dose toxicity studies of HP-β-CD, swollen and granular kidney tubular cells, swollen epithelial cells in the urinary bladder, an increase in Kupffer cells in the liver, etc. were observed in adult rats at ≥100 mg/kg (*Food Chem Toxicol*. 2005;43:1451-9); renal tubular vacuolation, vacuolation of urinary tract epithelial cells in the renal pelvis, ureter, and bladder, etc. were observed in juvenile rats at ≥50 mg/kg (*Reprod Toxicol*. 2015;56:87-96); and swollen epithelial cells of the urinary bladder and renal pelvis, increases in ALT, AST, and bilirubin, etc. were observed in dogs at ≥400 mg/kg (*Food Chem Toxicol*. 2005;43:1451-9).

PMDA's view:

Taking account of the seriousness of the disease for which an aqueous solution for intravenous infusion, "Prevymis Intravenous Infusion 240 mg," is indicated, and the results of assessment of different prototype formulations using other solubilizers,[1)] the use of HP-β-CD in Prevymis Intravenous Infusion 240 mg is unavoidable. However, since there is no adequate safety margin between the doses at which vacuolation of renal tubular epithelial cells, elevations of hepatic enzymes, etc. were observed in HP-β-CD toxicity studies in rats and dogs and the estimated maximum daily dose of HP-β-CD in clinical use (72 mg/kg), etc., HP-β-CD should be handled as a novel excipient.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The pharmacological effects of letermovir were evaluated in primary pharmacodynamic, secondary pharmacodynamic, safety pharmacology, and pharmacodynamic drug interaction studies. Unless otherwise specified, CMV refers to human CMV.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* antiviral activity

3.1.1.1 Antiviral activity against CMV laboratory strains

3.1.1.1.1 Antiviral activity against CMV laboratory strains (wild-type and mutant viruses) (Reference data, CTD 4.2.1.1.3[3)])

Normal human dermal fibroblast (NHDF) cells were infected with CMV strain AD169 or CMV AD169 variant carrying an amino acid substitution (M460I) in the UL97 protein[4)], and the antiviral activities of letermovir and ganciclovir (GCV) were determined by a cytopathic effect (CPE) reduction assay. The EC_{50} was defined as the concentration of test drug that inhibits the CPE by 50%. The EC_{50} values of letermovir against CMV strain AD169 and AD169-derived variant (mean) were 0.0051 and 0.0039 μmol/L, respectively, and the EC_{50} values of GCV were 2.4 and 12 μmol/L, respectively.

3) *Antimicrob Agents Chemother*. 2010;54:1290-7.
4) UL97 mutations confer resistance to GCV [Denosine 500 mg for Intravenous (IV) Infusion package insert (10th edition)].

3.1.1.1.2 Antiviral activity in various fibroblasts (Reference data, CTD 4.2.1.1.2)

Various fibroblasts were infected with green fluorescent protein (GFP)-expressing CMV strain AD169. The antiviral activity of each test drug was determined by a GFP-based fluorescence reduction assay, and the cytotoxicity of each test drug in the host cells was determined based on the fluorescence intensity. The EC_{50} was defined as the concentration of test drug producing 50% reduction in GFP units, and the 50% cytotoxic concentration (CC_{50}) was defined as the concentration of test drug reducing cell viability by 50% (the fluorescence from viable cells was quantified after addition of a reagent). The results are shown in Table 4.

Table 4. Antiviral activity in various fibroblasts and cytotoxic effect on host cells

Host cells	Test drug	EC_{50} (μmol/L)	CC_{50} (μmol/L)	Selectivity index (CC_{50}/EC_{50})
HS27 cells (Foreskin fibroblasts)	Letermovir	0.0056	107	19,107
	GCV	0.3190	>333	>1044
NHDF cells	Letermovir	0.0035	91	25,899
	GCV	1.9127	>333	>174
HELF cells (Embryonic lung fibroblasts)	Letermovir	0.0035	63	17,877
	GCV	2.3922	>333	>139
NHLF cells (Normal lung fibroblasts)	Letermovir	0.0050	64	12,903
	GCV	2.0650	>333	>161
MRC-5 cells (Fetal lung fibroblasts)	Letermovir	0.0045	127	28,015
	GCV	1.6490	>333	>202

Mean

3.1.1.1.3 Effect of multiplicity of infection (Reference data, CTD 4.2.1.1.2)

NHDF cells were infected with GFP-expressing CMV strain AD169, and the effect of multiplicity of infection on the antiviral activity of each test drug was determined by a GFP-based fluorescence reduction assay. The EC_{50} was defined as the concentration of test drug producing 50% reduction in GFP units. The results are shown in Table 5.

Table 5. Effect of multiplicity of infection on antiviral activity

MOI	EC_{50} value (μmol/L)	
	Letermovir	GCV
0.003	0.0013	0.9902
0.01	0.0015	0.6843
0.03	0.0029	1.7379
0.1	0.0034	2.2063
0.3	0.0036	6.5093
1	0.0042	5.2580

Mean MOI (Multiplicity of infection)

3.1.1.1.4 Effect of time from infection to drug exposure (Reference data, CTD 4.2.1.1.3[3])

NHDF cells were infected with GFP-expressing CMV strain AD169, and letermovir (50 nmol/L), GCV (20 μmol/L), or positive control [BAY38-4766 (11 μmol/L)] at approximately 10-fold the EC_{50} was added to the infected cells at 0 to 144 hours post-infection. At 7 days post-infection, GFP units of the infected cells were quantified to determine the effect of the time from infection to test drug exposure on the antiviral activity. GCV almost completely inhibited the proliferation in the infected cells when added up to 33 hours post-infection, whereas its inhibitory effect was decreased when added beyond 33 hours post-infection. Letermovir and BAY38-4766 almost completely inhibited the proliferation when added up to 57 hours (equivalent to a CMV replication cycle) post-infection, but their inhibitory effects were decreased when added later.

3.1.1.1.5 Effect of time of drug addition (before or after infection) (Reference data, CTD 4.2.1.1.7)

NHDF cells were infected with GFP-expressing CMV strain AD169. When letermovir or GCV was added 2 hours before or after infection, their antiviral activities were determined by a GFP-based fluorescence reduction assay. The EC_{50} was defined as the concentration of test drug producing 50% reduction in GFP units. The EC_{50} values of letermovir when added before and after infection were 0.0029 and 0.0025 μmol/L, respectively, and the EC_{50} values of GCV were 2.5 and 2.0 μmol/L, respectively. The EC_{50} values were similar, regardless of the time of drug addition, for both test drugs.

3.1.1.1.6 Effect of serum proteins (Reference data, CTD 4.2.1.1.2)

NHDF cells were infected with GFP-expressing CMV strain AD169, and the effect of serum proteins on the antiviral activity of each test drug was determined by a GFP-based fluorescence reduction assay. The EC_{50} was defined as the concentration of test drug producing 50% reduction in GFP units. The results are shown in Table 6.

Table 6. Effect of serum proteins on antiviral activity

Experiment	Serum protein	Concentration	EC_{50} (μmol/L)	
			Letermovir	GCV
A	Human serum	0% (not added)	0.0025	3.19
		5%	0.0035	3.07
		10%	0.0047	3.75
		20%	0.0056	5.73
		40%	0.0107	8.74
		100% (predicted)	0.0224	17.6
B	Not added	—	0.0035	3.66
	α1-acid glycoprotein	1 mg/mL	0.0208	1.14
	Human serum albumin	45 mg/mL	0.0021	2.62

Mean

3.1.1.2 Antiviral activity against clinical CMV isolates (CTD 4.2.1.1.6; Reference data, CTD 4.2.1.1.5[5])

NHDF cells or primary human fibroblasts were infected with clinical CMV isolates (74 isolates) from Germany, and the antiviral activities of letermovir and GCV were determined by a plaque reduction assay. The EC_{50} was defined as the concentration of test drug that reduces viral plaques by 50%. As to the antiviral activity of letermovir, the EC_{50} ratios of letermovir against these clinical isolates were 0.2 to 2.0 compared to the reference strain (Merlin strain; EC_{50}, 0.0031 μmol/L). Although 27 UL56 sequence variations[6] were identified from the clinical isolates, none of them had an impact on letermovir susceptibility.

The glycoprotein B (gB) genotype[7] of the isolates was determined, and the EC_{50} values of letermovir (mean) were 0.0023, 0.0022, 0.0022, and 0.0029 μmol/L against gB 1 (n = 29), gB 2 (n = 27), gB 3 (n = 11), and gB 4 (n = 3), respectively.

The EC_{50} values of letermovir against 50 clinical isolates obtained between 1995 and 2014 were low (0.00014-0.0057 μmol/L), and the applicant explained that there is no trend towards decreasing susceptibility to letermovir.

5) *Antiviral Res*. 2016;132:204-9.
6) R43K, T189M, L373I, A425V, I426T, S435A, M442T, S445N, N446 deletion, NSS449-451 deletion, T452I, S454N, G460V, A464T, G467A, V471A, V476A, E485G, V490E, E497G, D586N, S749N, V778A, S782F, V793A, P800L, and P803A
7) gB is a glycoprotein that is a component of the envelope and is required for CMV adsorption onto and entry into the host cells (*J Med Viol*. 2015;87:1737-48).

MRC-5 cells were infected with clinical CMV isolates from the US. The antiviral activities of letermovir and GCV were determined by a plaque reduction assay, and their cytotoxicity in the host cells was determined based on the absorbance after addition of a reagent. The EC_{50} was defined as the concentration of test drug that reduces viral plaques by 50%, and the CC_{50} was defined as the concentration of test drug that reduces the absorbance by 50%. The results are shown in Table 7.

Table 7. Antiviral activity against clinical CMV isolates and cytotoxic effect on host cells

Test drug	CMV strain	EC_{50} (μmol/L)	CC_{50} (μmol/L)	Selectivity index (CC_{50}/EC_{50})
Letermovir	14-4B	0.00888	>0.1	>11.3
	Coffman	0.0135		>7.41
	E. Mann	0.00771		>13.0
	C9207	0.00221		>45.2
	C9208	0.0180		>5.56
GCV	14-4B	8.06	>100	>12.4
	Coffman	7.36		>13.6
	E. Mann	11.5		>8.70
	C9207	4.25		>23.5
	C9208	12.1		>8.26
Mean				

3.1.1.3 Antiviral activity against various viruses (Reference data, CTD 4.2.1.1.4[8])

The EC_{50} values of letermovir against various herpesviruses (varicella zoster virus, herpes simplex virus 1 and 2, murine CMV, rat CMV, human herpesvirus 6, Epstein-Barr virus) were determined. The EC_{50} values were 4.5 μmol/L for murine CMV and >10 μmol/L for other viruses.[9]

The EC_{50} values of letermovir against various viruses other than herpesviruses were >10 μmol/L for human adenovirus 2 and influenza A virus, >11 μmol/L for human immunodeficiency virus type 1, >30 μmol/L for hepatitis B virus, and >32 μmol/L for hepatitis C virus replicon.[10]

3.1.2 Mechanism of action

3.1.2.1 Effects on CMV DNA replication and production of infectious viral particles (Reference data, CTD 4.2.1.1.1[11])

NHDF cells were infected with CMV strain AD169 and grown in the presence of letermovir (50 nmol/L), GCV (20 μmol/L), or vehicle at approximately 10-fold the EC_{50}. Then CMV DNA was quantified by real-time PCR. In the cells at ≥24 hours post-infection, GCV inhibited CMV DNA replication, while letermovir did not inhibit CMV DNA replication. The cell supernatants collected in these experiments were added to human foreskin fibroblast (HFF) cells and incubated. Then the production of infectious CMV particles was determined based on the number of infected cells. As a result, the number of infected cells was reduced in the supernatant

8) *Antimicrob Agents Chemother*. 2012;56:1135-7.

9) The EC_{50} against varicella-zoster virus, herpes simplex virus 2, murine CMV, and rat CMV were determined based on the number of plaques, the EC_{50} against human herpesvirus 6 was determined based on DNA levels, and the EC_{50} against herpes simplex virus 1 and Epstein-Barr virus were determined based on the fluorescence intensity. The EC_{50} was defined as the concentration of test drug that reduces viral plaques/DNA level/fluorescence intensity by 50%.

10) The EC_{50} against human adenovirus 2 was determined based on the number of plaques, the EC_{50} against hepatitis B virus was determined based on DNA levels, the EC_{50} against human immunodeficiency virus type 1 and influenza A virus were determined based on the fluorescence intensity, and the EC_{50} against hepatitis C virus was determined based on RNA levels. The EC_{50} was defined as the concentration of test drug that reduces viral plaques/DNA level/fluorescence intensity/RNA level by 50%.

11) *J Viol.* 2011;85:10884-93.

of cells treated with letermovir or GCV, indicating that letermovir and GCV inhibit the production of infectious CMV particles.

3.1.2.2 Effect on CMV DNA cleavage (Reference data, CTD 4.2.1.1.1[11])

Human embryonic lung fibroblast (HELF) cells were infected with CMV strain AD169 or CMV AD169 mutant carrying an amino acid substitution in UL56 of the terminase complex [CMV AD169-rAIC246-1, see Section 3.1.3.1] and incubated in the presence of letermovir or vehicle. Then, the isolated DNA was digested with a restriction enzyme, KpnI, and the cleavage of CMV DNA by the terminase complex was determined based on the size of DNA fragment.[12] In CMV DNA isolated from CMV AD169-infected cells, letermovir at 0.05 to 50-fold the EC_{50} (0.2-200 nmol/L) reduced the approximately 4-kB DNA fragment, compared to vehicle. In CMV DNA isolated from mutant virus-infected cells, no reduction occurred. This result indicated that letermovir inhibits the cleavage of CMV DNA by the terminase complex.

3.1.2.3 Effects on capsid maturation and production of viral particles (Reference data, CTD 4.2.1.1.1[11])

HFF cells were infected with CMV strain AD169 and grown in the presence of letermovir or vehicle. Then, capsid maturation and the production of viral particles were analyzed qualitatively by electron microscopy.[13] A capsids (empty capsids without DNA) and C capsids (genomic DNA-containing mature capsids) were reduced, and B capsids (capsids that contain scaffold proteins, but not DNA) became more abundant in the nuclei of letermovir-treated cells compared to vehicle-treated cells. No virus particle was found and only dense bodies (electron-dense particles comprised of a single tegument protein and an envelope) were observed in the cytoplasm of letermovir-treated cells compared to vehicle-treated cells. These results indicated that letermovir inhibits capsid maturation and the production of viral particles.

3.1.2.4 Effect on CMV protein synthesis (Reference data, CTD 4.2.1.1.1[11])

NHDF cells were infected with CMV strain AD169 and cultured in the presence of letermovir (50 nmol/L), GCV (20 μmol/L), or vehicle at approximately 10-fold the EC_{50}. Then, the expression of immediate-early, early, and late proteins of CMV was analyzed. GCV inhibited the expression of early and late proteins, whereas CMV protein expression was not affected by letermovir.

3.1.2.5 Assessment of reversibility of antiviral effect (Reference data, CTD 4.2.1.1.3[3])

In order to assess the reversibility of the anti-CMV activity of letermovir,[14] NHDF cells were infected with CMV strain AD169, and the production of infectious CMV particles after the removal of test drug was determined. After the infected cells were incubated in the presence or absence of letermovir (50 nmol/L) or GCV (20 μmol/L) at approximately 10-fold the EC_{50}, test drug was removed, and cell cultures were further

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12) Following restriction digestion, uncleaved concatemeric viral DNA yields an 8.4-kb *Kpn*I fragment, whereas terminase-cleaved concatemeric DNA results in a 4-kb fragment.

13) CMV capsids are classified into A capsids (empty capsids without DNA), B capsids (capsids that contain scaffold proteins, but not DNA), and C capsids (genomic DNA-containing mature capsids). The scaffold protein within B capsid is degraded and removed before or during DNA packaging, and DNA packaging leads to C capsid formation. A capsid is not a precursor of C capsid, and is formed as a result of failing to complete DNA packaging (*Intervirology*. 1996;39:389-400).

14) Penciclovir, which has anti-herpesvirus activity *in vitro*, has been reported to exhibit persistent activity even after the removal of the drug (*Antimicrob Agents Chemother*. 1987;31:1238-42).

incubated in fresh medium. The production of infectious CMV particles following the removal of letermovir and GCV increased over time and reached approximately 10^6 infectious units/mL at 48 and 72 hours, respectively, indicating that the antiviral effects of letermovir and GCV are reversible.

3.1.3 Resistance profile

3.1.3.1 Antiviral activity against selected mutants (Reference data, CTD 4.2.1.1.9,[15] 4.2.1.1.11,[16] 4.3:16[17])

NHDF cells were infected with CMV strain AD169 and incubated in the presence of letermovir.[18] Then, the antiviral activities of letermovir and GCV against CMV strain AD169 isolates were determined by a CPE assay, and mutations leading to amino acid substitutions in the terminase complex genes (UL56, UL89, UL104, and UL51)[19] were identified by DNA sequencing. The EC_{50} was defined as the concentration of test drug that inhibits the CPE by 50%, and the results are shown in Table 8. The applicant explained that an amino acid substitution (A345S) in the UL89 protein is present also in letermovir-susceptible strains, and should not impact the efficacy of letermovir.

Table 8. Antiviral activity against selected mutants and amino acid substitutions in terminase complex

CMV strain	EC_{50} (μmol/L)[a]		Resistance index[b]	Amino acid substitution			
	Letermovir	GCV		UL56	UL89	UL104	UL51
Wild-type (AD169)	0.0046	3.6					
rAIC246-1	1.23	1.2	268	L241P	—	—	—
rAIC246-2	0.37	4.0	81	R369S	A345S	—	—
rAIC246-3	27.23	3.0	5870	C325Y	—	—	—
rAIC246-4	0.13	4.2	28	V231L	—	—	—
rAIC246-5	0.11	5.0	23	R369M	—	—	—
rAIC246-6	0.08	2.9	17	R369M	—	—	—
rAIC246-7	0.92	2.2	200	L241P	—	—	—
rAIC246-8	25.01	2.2	5413	C325Y	—	—	—
rAIC246-9	0.06	1.7	13	R369G	—	—	—
rAIC246-10	0.09	1.4	19	V236M	A345S	—	—

—: Not detected.
a) Mean, b) letermovir EC_{50} for mutant virus/letermovir EC_{50} for wild-type virus

UL56 amino acid substitutions identified in the above experiments (V231L, V236M, L241P, C325Y, R369M, R369G, and R369S) were introduced into GFP-expressing CMV strain AD169. Using NHDF cells infected with the resulting recombinant viruses, the antiviral activity of each test drug was determined by a GFP-based, fluorescence reduction assay. The EC_{50} was defined as the concentration of test drug producing 50% reduction in GFP units. As a result, the resistance index [letermovir EC_{50} for mutant virus/letermovir EC_{50} for wild-type virus (0.0030 μmol/L)] was 5 to 8796.

UL56 amino acid substitutions (L134V/Q228H, V236M, D414N, S227I, and R410G)[20] identified in the clinical isolates from letermovir-treated subjects who had CMV viremia or CMV infection in a foreign phase II study [Study 020, see Section 7.1] were introduced into GFP-expressing CMV strain AD169. Using NHDF

15) *Antimicrob Agents Chemother*. 2014;58:610-13.
16) *J Infect Dis*. 2016;213:23-30.
17) *Antimicrob Agents Chemother*. 2015;59:6588-93.
18) NHDF cells infected with CMV strain AD169 were incubated in the presence of letermovir (at approximately 10-fold the EC_{50}), or CMV was subcultured, escalating the concentrations of letermovir.
19) As another CMV terminase inhibitor, BAY38-4766-resistant viruses have mutations in the terminase complex genes, these genes were sequenced to identify amino acid substitutions.
20) In a foreign late phase II study (Study 020), CMV DNA sequencing was successful for 27 samples from 12 letermovir-treated subjects who experienced CMV prophylaxis failure, and UL56 amino acid substitutions were identified.

cells infected with the resulting recombinant viruses, the antiviral activity of each test drug was determined by a GFP-based fluorescence reduction assay. The EC_{50} was defined as the concentration of test drug producing 50% reduction in GFP units. The resistance indices (variant EC_{50}/wild-type EC_{50} [0.0029 μmol/L]) were 46 for the V236M variant and 0.2 to 0.9 for other sequence variants. The replicative fitness of these virus mutants was assessed, and none of the introduced mutations impacted the fitness of the virus growth, compared to the wild-type strain.

HFF cells were infected with CMV strain T4138 and serially passaged, escalating the concentration of letermovir. Then, UL56 mutations detected were identified. The antiviral activity of letermovir against recombinant virus strains containing these mutations is shown in Table 9.

Table 9. Antiviral activity against recombinant virus strains

Amino acid substitution(s)	EC_{50} (μmol/L)[a)]	Fold change[b)]
Wild-type	0.0057	
L51M	0.0043	0.8
V231A	0.012	2.1
V236L	0.080	14
V236M + L257I + M329T	18	>3000
V236L + L257I	1.5	260
E237D	0.058	10
E237D + T244K + F261L	0.59	104
T244K	0.019	3.3
T244K + F261L	0.047	8.2
L257I	0.028	4.9
F261L	0.016	2.8
F261C	0.025	4.4
Y321C	0.026	4.6
C325F	21	>3000
C325R	20	>3000
M329T	0.025	4.4

a) Mean, b) letermovir EC_{50} for mutant virus/letermovir EC_{50} for wild-type virus

3.1.3.2 CMV UL56 and UL89 amino acid substitutions (CTD 4.2.1.1.10)

The deduced amino acid sequences for UL56 and UL89 proteins generated from entries in the CMV DNA sequence database of the National Center for Biotechnology Information (the US) were aligned with UL56 and UL89 amino acid sequences from CMV Merlin strain. The applicant explained that although there were variants at 44 amino acids of UL56, none of the previously-characterized UL56 letermovir-resistant genotypic variants in non-clinical and clinical studies of letermovir were found [see Section 3.1.3.1]. Although there were variants at 18 amino acids of UL89, none of these variants have been characterized for their impact on susceptibility to letermovir.

3.2 Secondary pharmacodynamics

3.2.1 Cytotoxicity in various cell lines (Reference data, CTD 4.2.1.2.1)

The CC_{50} values of letermovir in mouse, rat, and human cell lines[21)] ranged from 27 to >30 μmol/L.[22)] The CC_{50} of letermovir in MRC-5 cells was >0.1 μmol/L [see Section 3.1.1.2], and the CC_{50} values of letermovir in human foreskin, dermal, and lung fibroblasts were 63 to 127 μmol/L [see Section 3.1.1.1.2].

21) liver and kidney epithelial cells, heart muscle cells, embryo and dermal fibroblasts, monocytes, T-lymphocytes, macrophages, neuroblastoma and hepatoma cells

22) Determined based on the fluorescence intensity. The CC_{50} was defined as the concentration of test drug reducing cell viability by 50% (the fluorescence from viable cells was quantified after addition of a reagent).

3.2.2 Off-target effects (Reference data, CTD 4.2.1.2.2)

Letermovir (10 μmol/L) was analyzed in 63 radioligand-binding assays to evaluate potential off-target effects (interactions with receptors, ion channels, enzymes, etc.). No effects of letermovir were observed.

3.2.3 Effects on physiological functions (CTD 4.2.1.2.3)

The effects of letermovir (30 μmol/L) on various physiological functions were evaluated *in vitro*.[23)] Letermovir showed no inotropic effect in the isolated guinea pig left atria field stimulated at 1.5 Hz or no chronotropic effect in the isolated, spontaneously beating guinea pig right atria. Letermovir had no effects on potassium ion-induced contractions of the isolated rat aorta and portal vein and the isolated guinea pig ileum and trachea.

The effects of letermovir on various biological functions were evaluated in mice or rats after oral administration of letermovir 30 mg/kg.[23)] In mice, a 1.4-fold increase in blood glucose was observed at 90 minutes after dosing of letermovir, compared to vehicle. The applicant explained that this increase was of no toxicological significance. Letermovir had no effects on other physiological functions [mice: diarrhea, salivation, lacrimation, vasodilation, piloerection, behavior, mortality, body temperature, inhibitory symptoms, motor coordination, increased motor activity, the rate and depth of respiration, time to hemostasis, pupil size, serum total cholesterol, triglycerides and high-density lipoprotein, ALT, gastrointestinal motility; rats: mean arterial pressure at rest or following a change in posture, gastric acidity/gastric irritation (fasted rats), urine volume, sodium and potassium excretion].

3.3 Safety pharmacology (CTD 4.2.1.3.2, 4.2.1.3.4 to 4.2.1.3.11; Reference data, CTD 4.2.1.3.1, 4.2.1.3.3)

The effects of letermovir on the central nervous, cardiovascular, respiratory, renal/urinary, and gastrointestinal systems, etc. were assessed (Table 10).

[23)] A non-GLP, exploratory study was conducted in early phase development.

Table 10. Summary of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Doses or concentrations	Route of administration	Noteworthy findings
CNS	Rat (6M/group)	General symptoms, behavior, and body temperature	0, 5, 15, 45 mg/kg	Oral	Stereotypic chewing was observed in 1 animal (45 mg/kg group) at 1.5 and 2 hours post-dose.
	Rat (7 or 8M/group)	The convulsive threshold dose of pentylenetetrazole, the nocifensive responsiveness to heat, and hexobarbital-induced sleeping time	0, 5, 15, 45 mg/kg	Oral	A slight increase in the convulsive threshold dose of pentylenetetrazole at 5 mg/kg
Cardiovascular system	Human embryonic kidney cells (n = 3 or 4)[a)]	hERG current	0, 1, 10, 100 µmol/L	*In vitro*	IC_{50}, 68 µmol/L (38,900 ng/mL)
	Chinese hamster ovary cells (n = 5)	hERG current	8.9, 29, 86 µmol/L	*In vitro*	IC_{50}, 67 µmol/L (38,400 ng/mL)
	Conscious dog (5M or F/group)[a)]	Arterial blood pressure, heart rate, and ECG	0, 1, 3, 10 mg/kg	Oral	None
Cardiovascular and respiratory systems	Anesthetized dog (3M or F/group)	Hemodynamics, ECG, and respiratory function	0, 5, 15, 45 mg/kg	Intraduodenal	None
Renal/urinary system	Rat (10M/group)	Renal function, hematology, and lipid metabolism	0, 5, 15, 45 mg/kg	Oral	A dose-dependent increase in urinary sodium excretion
Gastrointestinal system	Rat (5M/group)	Gastrointestinal motility	0, 5, 15, 45 mg/kg	Oral	Dose-dependent delay of gastric emptying and increase in liquid intestinal contents
	Isolated guinea pig ileum (n = 4)	Contractility of the ileum	10^{-7}, 10^{-6} g/mL	*In vitro*	None
Others	Rat (6M/group)	Blood glucose levels	0, 5, 15, 45 mg/kg	Oral	None

a) Non-GLP study

The applicant's explanation about the effects of letermovir on the central nervous, cardiovascular, respiratory, renal/urinary, and gastrointestinal systems, etc.

As a CNS effect, stereotypic chewing was observed. Since this finding was observed only in 1 of 6 animals in the 45 mg/kg group and was transient, and this is a spontaneous behavior in rats, there is no particular problem. In repeated-dose toxicity studies, no effects on general symptoms/behavior were seen in monkeys (250 mg/kg/day group) and rats (100 mg/kg/day group) at exposures that were approximately 12- and 10-fold the C_{max} at the recommended clinical dose in HSCT recipients, respectively [see Section 5.2.7 and Section 5.2.5].

As cardiovascular effects, inhibition of hERG current was observed *in vitro* at a concentration that was approximately 137-fold higher than the human exposure at the recommended clinical dose in HSCT recipients (unbound C_{max} after IV administration of letermovir 480 mg, approximately 280 ng/mL).[24)] However, letermovir had no effects on ECG, etc. in a safety pharmacology study in anesthetized dogs (45 mg/kg group; 1-fold the C_{max} in HSCT recipients) and in a repeated-dose toxicity study in monkeys (250 mg/kg group; 1.5-fold the C_{max} in HSCT recipients) [see Section 5.2.7].

24) Estimated by the population pharmacokinetics (PPK) model built using the data from the global phase III study (Study 001). The steady-state C_{max} values at the recommended clinical dose in HSCT recipients were 4.5 µmol/L at oral doses of 480 mg, 38 µmol/L at IV doses of 480 mg, 6.8 µmol/L at oral doses of 240 mg (with concomitant cyclosporine), and 20 µmol/L at IV doses of 240 mg (with concomitant cyclosporine). Based on the highest C_{max} of 38 µmol/L (21,570 ng/mL) at IV doses of 480 mg and human plasma protein binding [98.7%, see Section 4.2.2], the unbound C_{max} was calculated.

As renal/urinary effects, a dose-dependent increase in urinary sodium excretion was observed in rats after administration of letermovir. The inter-individual variability of urinary sodium excretion was large, and its relationship to letermovir was unclear. This finding was considered of no toxicological significance.

As gastrointestinal effects, dose-dependent delay of gastric emptying and increase in liquid intestinal contents were observed in a study that evaluated the effects of letermovir on gastrointestinal motility in rats, but no effect of letermovir on intestinal transport distance of barium sulfate was observed. Repeated-dose toxicity studies in rats [see Section 5.2.3 and Section 5.2.4] showed no clinical observations indicative of gastrointestinal effects or histopathological changes in the gastrointestinal tract.

Based on the above, letermovir is unlikely to have effects on the central nervous, cardiovascular, respiratory, renal/urinary, and gastrointestinal systems, etc. in clinical use.

3.4 Pharmacodynamic drug interactions

3.4.1 Combination of letermovir with other anti-CMV drugs (Reference data, CTD 4.2.1.1.8[25])

The effects of letermovir combined with other anti-CMV drugs (GCV, cidofovir, foscarnet, or acyclovir) on GFP-expressing CMV AD169-infected NHDF cells were tested.[26] The combination of letermovir with each drug was additive, with no evidence of antagonism.

3.4.2 Combination of letermovir with anti-HIV drugs (Reference data, CTD 4.2.1.1.8[25])

The effects of letermovir (3.0 μmol/L) combined with various anti-HIV drugs[27] on GFP-expressing CMV AD169-infected NHDF cells or HIV-1 LAI-infected MT-4 cells were tested.[28] None of the combinations of letermovir with anti-HIV drugs significantly affected the anti-CMV activity of letermovir or the anti-HIV-1 activities of anti-HIV drugs.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activity of letermovir

The applicant's explanation about the change in the anti-CMV activity of letermovir over time and geographic differences:

The anti-CMV activity of letermovir was demonstrated in *in vitro* assays for antiviral activity [see Section 3.1.1]. There was no trend towards higher EC_{50} values of letermovir against the clinical isolates from Germany between 19[redacted] and 20[redacted], compared to the reference strain, showing no trend towards naturally occurring decreased susceptibility [see Section 3.1.1.2].

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25) *Antimicrob Agents Chemother*. 2015;59:3140-8.

26) Two techniques were used for analysis. (1) Using the Bliss independence model described by Prichard and Shipman (*Antiviral Res*. 1990;14:181-205), mean volumes [(μmol/L)^2%] were calculated. Values of <−50 indicate "antagonism," values of ≥−50 and ≤50 indicate "additive," and values of >50 indicate "synergism." (2) Using the Loewe additivity model described by Chou and Talalay (*Adv Enzyme Regul*. 1984;22:27-55), weighted average combination indices were calculated. Values of <0.8 indicate "synergism," values of ≥0.8 and ≤1.2 indicate "additivity," and values of >1.2 indicate "antagonism."

27) emtricitabine, tenofovir disoproxil fumarate, efavirenz, etravirine, nevirapine, rilpivirine, atazanavir, darunavir, lopinavir, ritonavir, raltegravir, and elvitegravir

28) EC_{50} of letermovir plus anti-HIV drug/EC_{50} of letermovir alone or EC_{50} of anti-HIV drug plus letermovir/EC_{50} of anti-HIV drug alone >2.5 was considered potential drug-drug interactions.

A literature review was conducted for gB polymorphism (gB is a gene product that may influence the virulence of CMV) (*Arch Virol*. 2008;153:667-74, *J Med Virol*. 2015;87:1441-5, etc.). According to the reports on the clinical isolates from Japan, gB 1 and gB 3 were more prevalent, and gB 2 and gB 4 were less prevalent. Similar results were obtained also for determination of the gB genotype of CMV isolates from Japanese subjects who experienced CMV viremia or CMV disease in a global phase III study [Study 001, see Section 7.2]. On the other hand, gB 2 was more prevalent among the clinical isolates from Germany, which was different from the distribution of gB genotypes among the clinical isolates from Japan [see Section 3.1.1.2]. Geographic (the US, Italy, and Africa) and demographic differences in the frequency of gB genotypes have been reported (*AIDS Res Hum Retroviruses*. 1998;14:533-6). Although the distribution of gB genotypes differed between Japan and overseas, as there were no apparent differences in letermovir susceptibility of CMV among any of the 4 gB genotypes [see Section 3.1.1.2], the geographic origin of CMV isolates is unlikely to impact the antiviral activity of letermovir.

CMV DNA sequences in the database of the National Center for Biotechnology Information (the US) were used to identify genetic variants in UL56 and UL89 leading to amino acid alterations. None of the previously-characterized UL56 letermovir-resistant genotypic variants in non-clinical and clinical studies of letermovir were found [see Section 3.1.3], and letermovir is not marketed in Japan or overseas as of July 2017, indicating that there is little concern about decreased susceptibility of CMV to letermovir at present.

PMDA's view:
Based on the submitted data, the anti-CMV activity of letermovir was demonstrated. Although the distribution of gB genotypes differed between Japan and overseas, given that the antiviral activity of letermovir against all gB genotypes was demonstrated etc., geographic differences in letermovir susceptibility are unlikely at present. However, since there is no information on genetic polymorphism associated with the virulence of CMV and letermovir susceptibility of clinical isolates from Japan, it is important to collect post-marketing information on these points, including the published literature, and promptly provide any new finding to healthcare professionals in clinical practice.

3.R.2 Mechanism of action and resistance profile of letermovir

The applicant's explanation about the mechanism of action and resistance profile of letermovir:
Once CMV infects the host cell, concatemeric DNA (a long continuous DNA molecule that contains multiple unit-length genomic DNAs) is replicated by CMV DNA polymerase in the nucleus. Concatemeric DNA is cleaved by the CMV DNA terminase complex (UL56, UL89, UL104, and UL51) and packaged into viral capsids. The mature viral capsid in the nucleus is translocated to the cytoplasm, acquires tegument proteins, and undergoes envelopment at the vesicles or the Golgi body, resulting in the formation of infectious particles, which egress to the extracellular space (*Virus Res*. 2009;143:222-34).

Mechanistic studies and studies on the resistance profile indicated that letermovir targets the UL56 subunit of the CMV DNA terminase complex, which is required for viral replication, and inhibits the cleavage of concatemeric DNA [see Section 3.1.2 and Section 3.1.3]. The studies also indicated that unlike GCV,

letermovir does not affect CMV DNA replication or protein synthesis [see Section 3.1.2.1 and Section 3.1.2.4] and that letermovir acts later in the viral replication cycle than GCV [see Section 3.1.1.1.4].

GCV and foscarnet, which are approved for the treatment of CMV disease in Japan, inhibit DNA polymerase to suppress CMV DNA replication (Denosine 500 mg for IV Infusion package insert [10th edition]), Foscavir Infusion Solution 24 mg/mL package insert [10th edition]). Since letermovir exhibits anti-CMV activity via a mode of action that differs from that of GCV or foscarnet, cross-resistance is not likely with these drugs. Letermovir was also shown to be active against GCV-resistant CMV AD169 variant carrying UL97 mutation [see Section 3.1.1.1].

In *in vitro* resistance selection experiments, amino acid substitutions in the UL56 subunit of the CMV DNA terminase complex (V231A/L, V236L/M, E237D, L241P, T244K, L257I, F261L/C, Y321C, C325F/R/Y, M329T, and R369G/M/S) conferred reduced susceptibility to letermovir [see Section 3.1.3.1].

In a foreign phase II study (Study 020), 6 amino acid substitutions in the UL56 protein (L134V, Q228H, V236M, D414N, S227I, and R410G) were identified in clinical isolates from letermovir-treated subjects who experienced CMV viremia or CMV disease, and V236M substitution conferred decreased susceptibility to letermovir [see Section 3.1.3.1]. In a global phase III study (Study 001), CMV DNA sequence analysis was performed on DNA isolated from plasma samples obtained from letermovir-treated subjects who experienced CMV viremia or CMV disease, and V236M and C325W substitutions in the UL56 protein (1 subject each) were identified. Although the C325W variant was not characterized for susceptibility to letermovir, amino acid substitutions at position C325 (C325Y/F/R) conferred reduced susceptibility to letermovir *in vitro*.

PMDA's view:
Based on the submitted non-clinical data, PMDA confirmed the mechanism of action of letermovir.

Amino acid substitutions in the UL56 subunit of the CMV DNA terminase complex (V231A/L, V236L/M, E237D, L241P, T244K, L257I, F261L/C, Y321C, C325F/R/Y, M329T, and R369G/M/S) affect CMV susceptibility to letermovir. Among which, V236M substitution and a substitution at position C325 (C325W substitution) were identified by CMV DNA sequence analysis performed on DNA isolated from plasma samples obtained from letermovir-treated subjects who experienced CMV viremia or CMV disease. However, since the information on CMV letermovir-resistance mutations obtained from clinical studies is limited, it is important to collect post-marketing information on letermovir-resistance mutations, including the published literature, and provide any new finding to healthcare professionals in clinical practice.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The PK of letermovir were studied in mice, rats, and monkeys after administration of radiolabeled letermovir or unlabeled letermovir. Plasma concentrations of letermovir were determined by liquid chromatography/tandem mass spectrometry (lower limit of quantification [LLOQ], 0.1-21 ng/mL). Radioactivity concentrations in biomaterials were determined by liquid scintillation counter or

accelerator mass spectrometry. Letermovir metabolites were measured by high performance liquid chromatography. Unless otherwise specified, PK parameters are expressed as the mean.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.1, 4.2.2.2.2)

Plasma PK parameters in rats and monkeys after a single oral or intravenous dose of letermovir (^{14}C-letermovir was administered at the 3 mg/kg oral dose in rats and at the 1 mg/kg IV dose in rats and monkeys, and unlabeled letermovir was administered in other cases) are shown in Table 11. The oral bioavailability of letermovir was 54.8% in the rat and 14.3% in the monkey.

Table 11. PK parameters after a single oral or intravenous dose of letermovir

Species	Route of administration	Dose (mg/kg)	Number of animals	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
Rat	P.O.	1	3M/time point	201	0.50	254	—	—	3.12
		3	3M/time point	652	0.50	1072	—	—	2.42
		10	3M/time point	2958	0.75	8521	—	—	1.28
	IV	0.3	3M/time point	282	—	139	2.15	3.01	—
		1	3M/time point	851	—	523	1.91	1.99	1.84
Monkey	P.O.	1	3F	19.1 ± 2.15	1.82 ± 1.74	138 ± 1.38	—	—	10.5 ± 1.21
		10	3F	510 ± 2.87	3.11 ± 1.58	2886 ± 1.88	—	—	10.7 ± 1.16
	IV	0.1	3F	263 ± 1.17	—	96.4 ± 1.10	1.04 ± 1.10	1.30 ± 1.83	4.91 ± 1.50
		1	3F	4432 ± 1.12	—	1380 ± 1.23	0.725 ± 1.23	1.59 ± 3.15	11.2 ± 2.82

Geometric mean or Geometric mean ± SD, V_{ss}: Steady-state volume of distribution, —: Not calculated

4.1.2 Repeated-dose studies (CTD 4.2.3.2.1, 4.2.3.2.5, 4.2.3.2.8, 4.2.3.2.11, 4.2.3.2.14)

PK parameters in mice, rats, and monkeys after repeated oral or intravenous doses of letermovir are shown in Table 12 and Table 13, respectively.

With respect to the dose-exposure relationship over the dose range tested, increased doses resulted in greater than dose-proportional increases in the AUC in both male and female rats and monkeys while there was no consistent trend in male and female mice. Concerning accumulation after multiple dosing, there was a trend towards decreased exposure (less than dose-proportional increases in exposure) in mice and monkeys and no increases or about a 2-fold increase in exposure in rats, after multiple dosing. As to gender-related differences, letermovir exposure was higher in male mice than in female mice on Day 1, but was largely similar between male and female mice at Week 13, letermovir exposure was lower in male rats than in female rats, and there were no apparent differences between male and female monkeys.

Table 12. PK parameters after repeated oral doses of letermovir

Species	Dose (mg/kg/day)	Number of animals	Sampling time point	C_{max} (μg/mL)		t_{max} (h)		AUC_{0-24} (μg·h/mL)	
				M	F	M	F	M	F
Mouse	40	3M and 3F/time point	Day 1	32.3	18.2	1.00	1.00	295	105
		3M and 3F/time point	Week 13	21.0	11.0	1.00	1.00	72.3	61.2
	100	3M and 3F/time point	Day 1	62.8	36.2	4.00	1.00	415	384
		3M and 3F/time point	Week 13	32.1	37.9	1.00	1.00	182	368
	250	3M and 3F/time point	Day 1	134	76.1	4.00	6.00	1275	585
		3M and 3F/time point	Week 13	57.4	56.2	6.00	4.00	349	366
Rat	17	3M and 3F/time point	Day 1	4.09	4.11	1.00	1.00	15.5	20.2
		3M and 3F/time point	Week 26	4.71	6.92	1.00	2.00	25.6	25.3
	50	3M and 3F/time point	Day 1	16.3	18.3	2.00	4.00	90.4	126
		3M and 3F/time point	Week 26	17.6	27.7	4.00	4.00	130	276
	150	3M and 3F/time point	Day 1	39.6	39.4	4.00	8.00	399	484
		3M and 3F/time point	Week 26	44.6	62.0	4.00	4.00	568	747
Monkey	30	4M and 4F	Day 1	4.89 ± 4.82	3.38 ± 2.14	2.00 ± 1.15	2.00 ± 1.15	15.8 ± 18.4	11.9 ± 7.10
		4M and 4F	Week 13	1.24 ± 0.86	1.57 ± 1.02	0.63 ± 0.25	1.50 ± 1.00	4.68 ± 1.50	6.63 ± 1.44
	100	4M and 4F	Day 1	52.9 ± 6.53	54.8 ± 17.1	3.75 ± 1.50	3.00 ± 0.00	431 ± 74.7	355 ± 121
		4M and 4F	Week 13	10.1 ± 9.79	16.8 ± 5.77	2.50 ± 1.00	2.50 ± 1.00	41.4 ± 29.7	74.3 ± 21.4
	300/250[a)]	6M and 6F	Day 1	123 ± 55.2	78.6 ± 41.4	7.17 ± 2.99	5.50 ± 4.04	1859 ± 979	1011 ± 888
		6M and 5F	Week 13	35.6 ± 16.3	26.8 ± 13.9	4.50 ± 3.67	5.40 ± 3.91	195 ± 64.4	166 ± 80.1

Mean or Mean ± SD

a) Due to adverse clinical signs in the 300 mg/kg group, the dose was lowered to 250 mg/kg on Day 11.

Table 13. PK parameters after repeated intravenous doses of letermovir

Species	Dose (mg/kg/day)	Number of animals	Sampling time point	C_0 (μg/mL)		AUC_{0-24} (μg·h/mL)	
				M	F	M	F
Rat	10	3M and 3F/time point	Day 1	7.47	8.00	11.3	15.6
		3M and 3F/time point	Day 28	14.1	23.4	22.5	28.7
	30	3M and 3F/time point	Day 1	34.2	45.0	97.3	148
		3M and 3F/time point	Day 28	43.0	74.2	117	150
	100	3M and 3F/time point	Day 1	120	142	661	876
		2 or 3M and 2 or 3 F/time point	Day 28	272	165	646	719
Monkey	10	3M and 3F	Day 1	36.4 ± 2.34	41.4 ± 4.47	15.7 ± 4.47	18.8 ± 2.26
		3M and 3F	Day 28	39.0 ± 7.95	35.1 ± 6.33	14.4 ± 3.53	15.9 ± 1.88
	30	3M and 3F	Day 1	105 ± 31.9	125 ± 21.7	102 ± 19.6	170 ± 67.3
		3M and 3F	Day 28	124 ± 23.9	155 ± 13.7	89.0 ± 11.7	109 ± 19.2
	100	5M and 5F	Day 1	277 ± 62.4	323 ± 96.1	978 ± 205	1017 ± 235
		5M and 5F	Day 28	224 ± 54.6	275 ± 25.1	435 ± 52.8	401 ± 77.2

Mean or Mean ± SD

4.1.3 *In vitro* cell permeability (CTD 4.2.2.3.1, 4.2.2.3.2)

The cell permeability of letermovir was evaluated in Caco-2 cells derived from colon carcinoma. The apparent permeability coefficient of letermovir (10 μmol/L) in the apical to basolateral direction ($P_{app\ A\rightarrow B}$) was 1.39 × 10^{-6} cm/s (Lucifer Yellow [a reference compound of low permeability], 0.673×10^{-6} cm/s). In another study using Caco-2 cells, the apparent permeability coefficient of letermovir (0.2-10 μmol/L) in the apical to basolateral direction ($P_{app\ A\rightarrow B}$) was 6.32 to 10.7 × 10^{-6} cm/s.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.3)

Tissue distribution of radioactivity[29] in albino rats (2 males [intravenous administration]) or 6 males [oral administration], 2 females [oral administration]) following a single oral or intravenous dose of ^{14}C-letermovir 3 mg/kg was determined by quantitative whole-body autoradiography. Following oral administration in male rats, highest concentrations of radioactivity were observed in the gastrointestinal content, bile duct, and liver, and radioactivity was widely distributed into the kidneys, lungs, heart, gastrointestinal tract, brain, etc. At 168 hours post-dose, tissue levels of radioactivity returned to background levels (defined as <8 Bq/mL), except for the renal cortex, medullary ray, liver, gastrointestinal content, and genital gland. Also following administration in female rats and intravenous administration, extensive distribution into different tissues was observed.

Tissue distribution of radioactivity was determined at 24 hours after a single oral dose of ^{14}C-letermovir 3 mg/kg in a pigmented rat (1 male). Tissue distribution of radioactivity in the pigmented rat was similar to that in albino rats, and there was no retention in melanin-containing tissues such as the eyes and pigmented skin.

4.2.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3.5, 4.2.2.3.7, 5.3.3.3.1, 5.3.3.3.2)

The extent of plasma protein binding of letermovir (0.2-50 μg/mL) was determined in plasma from mouse, rat, rabbit, dog, rhesus monkey, and human, using an ultrafiltration method. Letermovir was ≥97.3% protein-bound (the range of individual values at the concentrations tested) in all animal species tested, and 98.3% to 99.0% protein-bound in humans. The human plasma protein binding of letermovir was unchanged across a pH of 7.2-7.8.

The extent of plasma protein binding of letermovir (0.57 and 5.7 μg/mL) was determined in cynomolgus monkey plasma, using an equilibrium dialysis method. Letermovir was 97.4% and 94.8% protein-bound, respectively.

The extent of plasma protein binding was determined in subjects with renal impairment, subjects with hepatic impairment, and healthy subjects, using an equilibrium dialysis method. The plasma protein binding of letermovir in subjects with moderate (eGFR, 30-59 mL/min/1.73m^2) or severe (eGFR, <30 mL/min/1.73m^2) renal impairment (letermovir 120 mg QD for 8 days) (99.0% and 98.8%, respectively) was similar to that in healthy subjects (99.1%). The plasma protein binding of letermovir in subjects with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (letermovir 30 or 60 mg QD for 8 days) (98.9% and 98.6%, respectively) was similar to that in healthy subjects who received letermovir 30 or 60 mg QD (99.1% and 99.0%).

[29] In male albino rats, tissue distribution of radioactivity was determined at 2, 4, 8, 24, 72, and 168 hours after oral administration, or at 5 minutes and 2 hours after intravenous administration. In female albino rats, tissue distribution of radioactivity was determined at 2 and 24 hours after oral administration.

In the presence of human serum albumin (40 g/L) and α1-acid glycoprotein (0.7 g/L), the protein binding of letermovir was 94.8% and 78.1%, respectively.

The rat, dog, monkey, and human blood to plasma ratios of letermovir (0.1-10 μg/mL) were 0.64, 0.49, 0.61, and 0.56, respectively, and independent of the concentrations tested.

4.2.3 Placental transfer (CTD 4.2.2.3.4)

Following a single oral dose of ^{14}C-letermovir 3 mg/kg in albino rats (5 females) on gestation day 18, radioactivity concentrations in maternal and fetal tissues were determined. In fetal tissues tested,[30)] radioactivity was detected at 1 to 8 hours post-dose, and highest concentrations were observed at 4 hours post-dose. Radioactivity was detected in maternal placenta and uterus at 1 to 24 hours post-dose. Radioactivity was below the LLOQ in the amniotic fluid up to 8 hours post-dose, but low concentrations of radioactivity were detected at 24 hours post-dose (0.010 μg eq./g).

4.3 Metabolism

4.3.1 Proposed metabolic pathways

Based on the considerations in Section 4.3.2 and Section 4.3.3, the proposed metabolic pathways of letermovir are shown in Figure 1.

[30)] blood, brain, eyes, intestinal tract, kidneys, liver, lungs, myocardium, skin, uvea

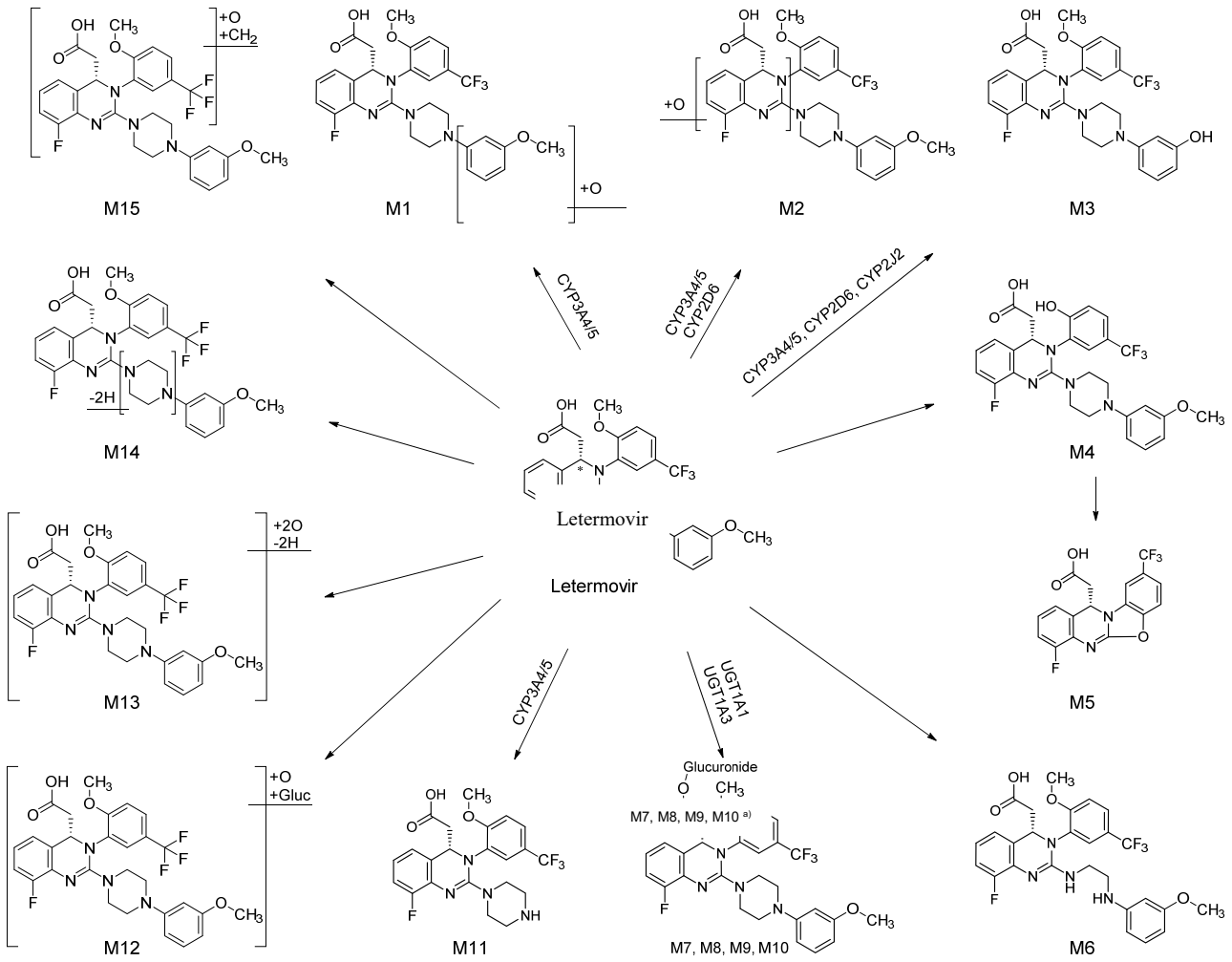

Figure 1. Proposed metabolic pathways of letermovir (Cited from CTD 2.6.5.20)
a) M8, M9, and M10 are drug glucuronide isomers.

4.3.2 *In vitro* metabolism (CTD 4.2.2.4.1, 4.2.2.4.4, 4.2.2.6.7)[31)]

Mouse, rat, rabbit, dog, monkey, and human liver microsomes or primary hepatocytes were added with ^{14}C-letermovir (at a final concentration of 5 or 20 μmol/L), and the metabolites of letermovir were identified. The results are shown in Table 14.

Table 14. Species distribution of letermovir metabolites detected in *in vitro* studies

Species	Test system using liver microsomes	Test system using hepatocytes
Mouse	Parent compound, M1, M2	Parent compound, M1, M7, M8, M9, M11, M12, M13, M14
Rat	Parent compound, M1, M2, M4, M14	Parent compound, M2, M3, M6, M7, M8, M9, M11, M12, M14
Rabbit	Parent compound, M1, M2, M4, M5, M11, M14	Parent compound, M5, M7, M8, M9
Dog	Parent compound, M1, M2, M3, M6, M14	Parent compound, M7, M8, M9, M11, M15
Monkey	Parent compound, M1, M2, M3, M4, M14	Parent compound, M7, M8, M9, M11, M14
Human	Parent compound, M1, (M10)[a)]	Parent compound, M2, M3, M7, M8, M9, M11

a) An acyl-glucuronide metabolite detected in a study using microsomes expressing human recombinant UGT isoforms (UGT1A1 and UGT1A3)

The metabolism of letermovir was studied using human liver microsomes and the human recombinant CYP expression system (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9-Arg, CYP2C9-Cys, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, and CYP4A11). When human liver microsomes

31) The metabolites listed in this section are as follows: M1 (a product of hydroxylation), M2 (a product of oxidation), M3 (a product of O-demethylation), M4 (a product of oxidative O-demethylation), M5 (a metabolite resulting from nucleophilic substitution of M4), M6, M11, and M14 (products of N-dealkylation), M7, M8, M9, and M10 (acyl-glucuronide metabolites), M12 (a product of oxidative glucuronidation), M13 (a product of oxidation), M15 (a product of oxidative methylation)

were added with ^{14}C-letermovir (at a final concentration of 9.9 μmol/L), the metabolism of letermovir was completely inhibited by a non-specific CYP inhibitor, 1-aminobenzotriazole. CYP2C8/3A, CYP3A, and CYP2C9 inhibitors inhibited the metabolism of letermovir by 44.6%, 81.9% to 85.7%, and 27.7%, respectively. On the other hand, CYP1A2, CYP2C19, CYP2D6, and CYP2E1 inhibitors caused no marked inhibition.[32)] In the CYP expression system, letermovir was metabolized primarily by CYP3A4 and CYP3A5, and CYP2D6 and CYP2J2 were also involved in the metabolism of letermovir.

The metabolism of letermovir was studied using the human recombinant UGT expression system (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17). When ^{14}C-letermovir (at a final concentration of 9.9 or 99.2 μmol/L) was added, UGT1A1 and UGT1A3 were suggested to be major contributors to the formation of an acyl-glucuronide metabolite (M7).

4.3.3 *In vivo* metabolism (CTD 4.2.2.4.3, 5.3.3.1.7)

Following a single intravenous or oral dose of ^{14}C-letermovir 3 mg/kg in bile duct cannulated and intact rats (5 males each), the metabolites listed in Table 15 were detected in bile, feces, and urine.

The applicant's explanation:
M7 detected in bile from bile duct cannulated rats was not present in feces from intact rats, suggesting that the acyl-glucuronide metabolite is hydrolyzed in the gastrointestinal tract.

Table 15. *In vivo* metabolism (Rat)

	Bile duct cannulated rats[a)]	Intact rats[b)]
Bile	Parent compound (IV, 15.7%; oral, 8.3%) M1 (IV, 21.7%; oral, 7.7%) M7 (IV, 21.3%; oral, 35.5%) Structurally uncharacterized metabolites (IV, 33.4%; oral, 26.1%)	Not determined
Feces	Parent compound (IV, 1.4%; oral, 4.8%) M1 (IV, 0.6%; oral, 4.3%) Structurally uncharacterized metabolites (IV, 0.2%; oral, 6.2%)	Parent compound (IV, 14.7%; oral, 11.4%) M1 (IV, 23.7%; oral, 19.7%) Structurally uncharacterized metabolites (IV, 53.8%; oral, 59.8%)
Urine	Parent compound (IV, 0.10%) M1 (IV, 0.01%) Structurally uncharacterized metabolites (IV, 0.08%)	Not determined

a) up to 24 hours post-dose for bile and feces, up to 8 hours post-dose for urine (IV administration only), b) up to 48 hours post-dose

Following a single intravenous dose of ^{14}C-letermovir 1 mg/kg or a single oral dose of ^{14}C-letermovir 3 mg/kg in rats (3 males/time point), the parent compound represented the majority of radioactivity in plasma up to 24 hours post-dose, the major metabolite was M5, and M5 accounted for approximately 25% of the AUC of plasma radioactivity.

When healthy men (8 subjects) received oral unlabeled letermovir 80 mg BID for 4 days and unlabeled letermovir 80 mg and ^{14}C-letermovir (12 kBq) on Day 5, 96.6% of radioactivity in plasma up to 48 hours post-dose was attributed to the parent compound, and the remaining radioactivity to 3 structurally uncharacterized metabolites. M5 present in rat plasma was not detected in human plasma. In feces (up to 24-96 hours post-dose), the parent compound (70.5%) was the major component, and M7 (6.0%) and 4 structurally uncharacterized metabolites (4% each) were observed.

32) The following compounds were used as CYP inhibitors: CYP1A2, furafylline; CYP2C8, quercetin; CYP2C9, sulfaphenazole; CYP2D6, quinidine; CYP2E1, 4-methylpyrazole; CYP2C19, benzylphenobarbital; CYP3A, azamulin, ketoconazole

4.4 Excretion

4.4.1 Urinary and fecal excretion and biliary excretion (CTD 4.2.2.2.2, 4.2.2.5.1, 5.3.3.1.7)

The excretion of letermovir was studied in bile duct cannulated rats (4 males each) and intact rats (5 males each) following a single intravenous or oral dose of ^{14}C-letermovir 3 mg/kg. In intact rats, 93.8% of radioactivity (92.9% in feces, 0.8% in urine) after IV administration and 92.4% of radioactivity (91.4% in feces, 0.6% in urine) after oral administration were recovered by 168 hours post-dose. In bile duct cannulated rats, 95.9% of radioactivity (92.1% in bile, 2.24% in feces, 0.2% in urine) after IV administration and 98.5% of radioactivity (77.6% in bile, 15.3% in feces, 0.1% in urine) after oral administration were recovered by 24 hours post-dose.

Following a single intravenous dose of ^{14}C-letermovir 1 mg/kg in monkeys (3 females), 92.0% of radioactivity (86.9% in feces, 4.1% in urine) was recovered by 168 hours post-dose.

When healthy men (8 subjects) received oral unlabeled letermovir 80 mg BID for 4 days and unlabeled letermovir 80 mg and ^{14}C-letermovir (12 kBq) on Day 5, 94.7% of radioactivity (93.3% in feces, 1.4% in urine) was recovered by 336 hours post-dose.

4.4.2 Excretion into milk (CTD 4.2.2.5.3)

Lacteal secretion of letermovir was evaluated in lactating rats on postpartum day 10 (3/time point) following a single dose of letermovir 10 mg/kg. The letermovir concentrations in milk were 671, 364, 31.4, and 3.9 ng/mL at 2, 4, 8, and 12 hours post-dose, respectively.

4.5 Pharmacokinetic drug interactions

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.6.2, 4.2.2.6.4, 4.2.2.6.6, 4.2.2.6.19)

The potential of letermovir to inhibit CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5)[33)] and UGT isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7)[34)] was evaluated using human liver microsomes. The IC_{50} values of letermovir for CYP2B6, CYP2C8, and UGT1A1 were 54, 0.34, and 14 μmol/L, respectively, and letermovir inhibited CYP2B6 (Ki value, 38 μmol/L), CYP2C8 (Ki value, 0.22 μmol/L), and UGT1A1 (Ki value, 16 μmol/L) *in vitro*. The IC_{50} values of letermovir for other CYP isoforms and UGT isoforms were >100 μmol/L. Letermovir was also evaluated as a time-dependent inhibitor of these CYP isoforms. Letermovir was a time-dependent inhibitor of CYP3A (concentration at 50% of maximal inactivation [K_I], 35 μmol/L; maximal inactivation constant [k_{inact}], 0.0437 min^{-1} [substrate, midazolam]), but caused no time-dependent inhibition of other CYP isoforms.

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33) The following compounds were used as substrates for different isoforms: CYP1A2, phenacetin; CYP2A6, coumarin; CYP2B6, efavirenz; CYP2C8, amodiaquine; CYP2C9, diclofenac; CYP2C19, (*S*)-mephenytoin; CYP2D6, dextromethorphan; CYP2E1, chlorzoxazone; CYP3A4/5, testosterone, midazolam

34) The following compounds were used as substrates for different isoforms: UGT1A1, 17 β-estradiol; UGT1A4, trifluoperazine; UGT1A6, 1-naphthol; UGT1A9, propofol; UGT2B7, morphine

The applicant's explanation:
Based on the above results, taking account of letermovir exposure at the recommended clinical dose in HSCT recipients,[35] the plasma protein binding, the maximal theoretical concentration in the gut, predictions based on a static pharmacokinetic model, etc., letermovir, regardless of route of administration, inhibits CYP2C8, CYP3A, and UGT1A1 in the liver, and orally administered letermovir may inhibit CYP3A and UGT1A1 in the intestine, in clinical use.

The potential of letermovir (0.1-20 μmol/L) to induce the activities and mRNA expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4)[36] was evaluated in cultured human primary hepatocytes. Letermovir increased CYP3A4 mRNA levels, but did not increase its activity. Increases in CYP2B6 mRNA levels and activity were observed. No induction of CYP1A2 was observed over the concentration range tested.

As a surrogate marker for hepatic enzyme induction, the production of CYP3A64 mRNA was evaluated in cynomolgus monkey hepatocytes following exposure to letermovir. Letermovir (0.1-30 μmol/L) concentration-dependently increased CYP3A64 mRNA levels.

The applicant's explanation based on the above results:
Induction of CYP3A4 and CYP2B6 observed in the *in vitro* study are likely to be mediated by nuclear receptors, the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR), and PXR and CAR are known to activate the expression of metabolizing enzymes such as CYP3A4, CYP2B6, CYP2C9, and CYP2C19 and transporters (*Drug Metab Pharmacokinet*. 2008;23:45-53, *Adv Drug Deliv Rev*. 2010;62:1238-49, *Cancer Chemother Pharmacol*. 2010;66:765-71, etc.). Thus, letermovir may cause PXR- and CAR-mediated induction of metabolizing enzymes such as CYP3A4, CYP2B6, CYP2C9, and CYP2C19 and transporters in humans.

4.5.2 Evaluation of letermovir as a substrate of drug transporters (CTD 4.2.2.6.1, 4.2.2.6.3, 4.2.2.6.13, 4.2.2.6.14, 4.2.2.6.18)

Using Chinese hamster ovary (CHO) cells expressing OATP1B1, OATP1B3, OATP2B1, OCT1, or OAT1, which are hepatic uptake transporters, letermovir was evaluated as a potential substrate for these transporters. The accumulation of ^{14}C-letermovir (0.5 and 5 μmol/L) in OATP1B1- or OATP1B3-expressing cells was higher than that in the parental cells. There were no apparent differences in the accumulation of letermovir between the cells expressing OATP2B1, OCT1, or OAT1 and the parental cells. An OATP1B1 substrate (estrone-3-sulfate) and an OATP1B1 inhibitor (cerivastatin) (0.14-100 μmol/L each) inhibited the uptake of ^{14}C-letermovir (0.5 μmol/L) in OATP1B1-expressing cells by 73% and 70%, respectively, and the IC_{50} values were 2.8 and 7.7 μmol/L, respectively. An OATP1B3 substrate (Fluo-3, 0.10-100 μmol/L) and an OATP1B3 inhibitor (fluvastatin, 0.10-300 μmol/L) inhibited the uptake of ^{14}C-letermovir (0.15 μmol/L) by OATP1B3-expressing cells by 86% and 100%, respectively, and the IC_{50} values were 32 and 11 μmol/L, respectively.

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35) The steady-state C_{max} values at the recommended clinical dose in HSCT recipients, estimated by the PPK model built using the data from the global phase III study (Study 001), were 4.5 μmol/L at oral doses of 480 mg, 38 μmol/L at IV doses of 480 mg, 6.8 μmol/L at oral doses of 240 mg (with concomitant cyclosporine), and 20 μmol/L at IV doses of 240 mg (with concomitant cyclosporine).

36) The following compounds were used as substrates for different isoforms: CYP1A2, phenacetin; CYP2B6, bupropion; CYP3A4, testosterone

Using membrane vesicles from Sf9 insect cells expressing human P-glycoprotein (P-gp), multidrug resistant-associated protein (MRP2), breast cancer resistance protein (BCRP), or bile salt export pump (BSEP), letermovir was evaluated as a potential substrate for these transporters. The accumulation of ^{14}C-letermovir (10 and 100 μmol/L) in the membrane vesicles from BSEP-expressing cells was 1.2 to 1.4-fold higher in the presence of ATP than in the absence of ATP. On the other hand, no accumulation in the membrane vesicles from P-gp-, MRP2-, or BCRP-expressing cells was observed, either in the presence or absence of ATP.

Using Madin-Darby canine kidney (MDCK II) cells expressing human BCRP, letermovir was evaluated as a potential substrate for BCRP. The efflux ratio of letermovir (1 μmol/L) in BCRP-expressing cells relative to the parental cells was 2.0, which was reduced to 0.75 in the presence of a BCRP inhibitor, Ko143.

Using Lilly laboratories cell - porcine kidney (LLC-PK1) cells expressing human P-gp, letermovir was evaluated as a potential substrate for P-gp. The efflux ratios of ^{14}C-letermovir (0.1 and 1 μmol/L) in P-gp-expressing cells relative to the parental cells were 21.3 and 13.9, respectively.

The above results suggested that letermovir may be a substrate of OATP1B1, OATP1B3, P-gp, BCRP, and BSEP.

4.5.3 Evaluation of letermovir as an inhibitor of drug transporters (CTD 4.2.2.6.1, 4.2.2.6.13, 4.2.2.6.14)

Using membrane vesicles from Sf9 insect cells expressing human P-gp, MRP2, BCRP, or BSEP, letermovir was evaluated as a potential inhibitor of these transporters. Letermovir (0.14-100 μmol/L) inhibited the uptake of a P-gp substrate (N-methyl-quinidine), an MRP2 substrate (estradiol-17-β-D-glucuronide), a BCRP substrate (methotrexate), and a BSEP substrate (taurocholic acid) into the membrane vesicles, and the IC_{50} values were 13.7, 47.2, 29.1, and 30.4 μmol/L, respectively.

Using MDCK II cells expressing OATP1B1 or OATP1B3, human hepatic uptake transporters, letermovir was evaluated as a potential inhibitor of OATP1B1 and OATP1B3. Letermovir (0-25 μmol/L) inhibited the cellular uptake of an OATP1B1 substrate (pitavastatin) and an OATP1B3 substrate (sulfobromophthalein), and the IC_{50} values were 2.9 and 1.1 μmol/L, respectively.

Using CHO cells expressing OATP1B1, OATP1B3, OATP2B1, or OCT1, human hepatic uptake transporters, letermovir was evaluated as a potential inhibitor of these transporters. Letermovir (0.14-100 μmol/L) inhibited the cellular uptake of an OATP1B1 substrate (estrone-3-sulfate), an OATP1B3 substrate (Fluo-3), an OATP2B1 substrate (estrone-3-sulfate), and an OCT1 substrate (tetraethylammonium chloride), and the IC_{50} values were 13, 2.2, 30, and 65 μmol/L, respectively.

Using MDCK II or CHO cells expressing OAT1, OAT3, or OCT2, human renal uptake transporters, letermovir was evaluated as a potential inhibitor of OAT1, OAT3, and OCT2. Letermovir (0-25 μmol/L) inhibited the cellular uptake of an OAT3 substrate (estrone-3-sulfate), and the IC_{50} value was 2.5 μmol/L. Letermovir (100

μmol/L) inhibited the cellular uptake of an OAT1 substrate (p-aminohippuric acid) and an OCT2 substrate (metformin) by approximately 50%.

The applicant's explanation:
Based on the above results, taking account of letermovir exposure at the recommended clinical dose in HSCT recipients,[35] the protein binding, the maximal theoretical concentration in the gut, etc., letermovir in clinical use may inhibit P-gp, MRP2, BCRP, and BSEP in the liver, regardless of route of administration; P-gp and BCRP in the intestine after oral administration; and OATB1B3 and OAT3 after intravenous administration.

4.R Outline of the review conducted by PMDA

Concerning PK based on the results from letermovir non-clinical studies submitted, PMDA reviewed the precautionary statements etc. in the package insert (draft), and concluded that there is no particular problem.

5. Toxicity and Outline of the Review Conducted by PMDA

Single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, local tolerance, and other toxicity (a phototoxicity study) studies were conducted. The applicant explained that as there is no known mammalian counterpart of the viral terminase complex, which is the pharmacological target of letermovir (*Rev Med Virol*. 2002;12:115-27), no toxicities related to the pharmacological effects of letermovir should occur. In toxicity studies, the monkey was selected as a non-rodent species based on exposure after oral administration of letermovir.

Unless otherwise specified, 0.5% (w/v) aqueous methyl hydroxyethyl cellulose was used as a vehicle in *in vivo* studies.

5.1 Single-dose toxicity (CTD 4.2.3.1.1)

The acute oral and intravenous toxicity of letermovir was assessed in mice and rats.

A single oral dose of letermovir 2000 mg/kg was administered to naval medical research institute (NMRI) mice (6 females) and Wistar rats (6 females). Decreased motility, piloerection, narrowed palpebral fissure, and diarrhea were observed in mice. One of the 6 rats died, and piloerection, increased water consumption, and diarrhea were observed in rats. Based on the above, the approximate lethal doses by oral route were determined to be >2000 mg/kg in mice and 2000 mg/kg in rats.

A single IV dose of letermovir (vehicle, polyethylene glycol 400) 30 or 200 mg/kg was administered to NMRI mice (3 or 6 females/group) and Wistar rats (3 or 6 females/group). In both mice and rats, abdominal position, tremor, decreased motility, narrowed palpebral fissure, and signs of local irritancy at the injection sites, including blue colored tail and lost tail, were observed at both dose levels, and all animals died with convulsions and labored breathing at 200 mg/kg. Based on the above, the approximate lethal dose by IV route was determined to be 200 mg/kg in both mice and rats.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in mice (13 weeks), rats (4 weeks, 13 weeks, 26 weeks), and monkeys (4 weeks, 13 weeks, 39 weeks) and repeated intravenous dose toxicity studies in rats (28 days) and monkeys (28 days) were conducted. The major toxicological findings were seminiferous tubule degeneration and oligospermia in the epididymis in rats and gastrointestinal disorders such as salivation, emesis, inappetence, and soft feces in monkeys.

The $AUC_{0\text{-}24}$ values at 50 mg/kg in the rat 26-week oral toxicity study and at the no-observed-adverse-effect-level (NOAEL) (100 mg/kg) in the monkey 39-week oral toxicity study (203 and 46.4 μg·h/mL, respectively) were 2.0- and 0.5-fold the $AUC_{0\text{-}24}$ (100 μg·h/mL) at the recommended clinical IV dose in HSCT recipients,[37] respectively and 3.3- and 0.8-fold the $AUC_{0\text{-}24}$ (60.8 μg·h/mL) at the recommended clinical oral dose in HSCT recipients,[37] respectively.

5.2.1 Thirteen-week oral toxicity study in mice (CTD 4.2.3.2.1)

ICR mice (12/sex/group) were orally treated with letermovir 0 (vehicle), 40, 100, or 250 mg/kg for 13 weeks. Centrilobular hepatocellular hypertrophy associated with increased liver weights, which was considered an adaptive response to letermovir exposure, and adrenal cortical hypertrophy, which was considered secondary to stress, at ≥40 mg/kg, decreased body weight gain at ≥100 mg/kg, and transient mouth rubbing, increases in ALT, AST, globulin, and total bilirubin, decreases in albumin, the albumin/globulin ratio, potassium, creatinine, and cholesterol, and hepatocyte vacuolation at 250 mg/kg were observed.

Based on the above, the NOAEL was determined to be 100 mg/kg.

5.2.2 Four-week oral toxicity study in rats (CTD 4.2.3.2.3)

Wistar rats (10/sex/group) were orally treated with letermovir 0 (vehicle), 20, 60, or 180 mg/kg for 4 weeks. In this study, immunotoxicity endpoints (splenocyte immunophenotyping, splenic cell count, serum IgG, IgM, and IgA antibody titers) were also evaluated. Spermatic exfoliation in the seminiferous tubules, spermatic retention, and vacuolation of the tubular epithelium in the testes and spermatic debris and oligospermia in the epididymides were observed at 180 mg/kg. Immunotoxicity evaluation revealed changes in splenocyte subpopulations (decreased CD8+ T cells, increased B cells and antigen-presenting cells) at 180 mg/kg. The applicant explained that these findings are considered of little toxicological significance because these changes were minimal and there were no findings indicative of immunotoxicity in other test parameters.

Based on the above, the NOAELs were determined to be 60 mg/kg in males and 180 mg/kg in females.

5.2.3 Thirteen-week oral toxicity study in rats (CTD 4.2.3.2.4)

Wistar rats (10 or 20/sex/group) were orally treated with letermovir 0 (vehicle), 20, 60, or 180 mg/kg for 13 weeks. A 4-week recovery period following the dosing period was scheduled for some animals. In this study,

[37] The $AUC_{0\text{-}24}$ values after administration of letermovir in HSCT recipients, estimated by the PPK model built using the data from the global phase III study (Study 001), were 34.4 μg·h/mL at oral doses of 480 mg, 100 μg·h/mL at IV doses of 480 mg, 60.8 μg·h/mL at oral doses of 240 mg (with concomitant cyclosporine), and 70.3 μg·h/mL at IV doses of 240 mg (with concomitant cyclosporine) [see Section 6.2.5.2].

immunotoxicity endpoints (splenocyte immunophenotyping, splenic cell count, serum IgG, IgM, and IgA antibody titers, and plaque-forming cell assay for T-cell dependent antibody response testing) were also evaluated. Increased liver weights, which was considered an adaptive response to letermovir exposure, at ≥60 mg/kg and decreased testis and epididymis weights, germinal epithelium degeneration in the testes, oligospermia and increased spermatic debris in the epididymides, and hepatocellular hypertrophy and centrilobular fat deposition, which were considered an adaptive response to letermovir exposure, at 180 mg/kg were observed. All findings were reversible following a recovery period. Immunotoxicity evaluation revealed decreased CD45 high cells and increased CD45 low cells and T-helper cells at ≥60 mg/kg and increases in B cells, antigen-presenting cells, CD45 total cells, and splenic cell counts at 180 mg/kg. The applicant explained that these findings are considered of little toxicological significance because these changes were minimal and there were no findings indicative of immunotoxicity in other test parameters.

Based on the above, the NOAELs were determined to be 60 mg/kg/day in males and 180 mg/kg in females.

5.2.4 Twenty-six-week oral toxicity study in rats (CTD 4.2.3.2.5)

Wistar rats (15/sex/group) were orally treated with letermovir 0 (vehicle), 17, 50, or 150 mg/kg for 26 weeks. A 4-week recovery period following the dosing period was scheduled for some animals. Decreases in food consumption and body weight gain were noted at ≥50 mg/kg. The applicant explained that these findings are considered of little toxicological significance because there were no associated changes in observations/examinations. Seminiferous tubular vacuolation and atrophy were observed at 150 mg/kg. The applicant explained that these findings were incidental based on the number of animals with these findings, the incidence of these histopathological changes in the testes in the vehicle group, the laboratory's historical data, etc. No letermovir-related changes were seen after a recovery period.

Based on the above, the NOAEL was determined to be 150 mg/kg. In this study, no letermovir-related testicular effects were observed, and its reason is unknown. The applicant explained that since the AUC_{0-24} at 150 mg/kg (568 μg·h/mL) was higher than the AUC_{0-24} at 180 mg/kg causing testicular effects in the rat 13-week repeated-dose toxicity study (330 μg·h/mL), the exposure at 150 mg/kg may cause testicular effects.

5.2.5 Twenty-eight-day intravenous toxicity study in rats (CTD 4.2.3.2.8)

Wistar rats (10/sex/group) were intravenously treated with letermovir 0 [vehicle, 30% (w/v) HP-β-CD in a 5% (w/v) glucose solution], 10, 30, or 100 mg/kg for 28 days. A 2-week recovery period following the dosing period was scheduled for some animals. As HP-β-CD-related effects, vacuolation of tubular epithelial cells in the cortex and the outer stripe of the medulla in the kidneys and foamy alveolar macrophages in the lungs were observed in both the vehicle and letermovir groups. The incidence and severity of these findings in the letermovir groups were similar to those in the vehicle group. Transient decreased activity, labored breathing, mouth rubbing, swollen tail, decreased testis/epididymis weights, germinal epithelium degeneration, spermatid retention, and tubular vacuolation in the testes, and oligospermia and spermatic debris in the epididymides at 100 mg/kg were observed. The applicant explained that decreased activity, labored breathing, mouth rubbing, and swollen tail are considered of little toxicological significance because these

findings were transient and not associated with other clinical signs. After a recovery period, small epididymis, soft testis, small testis, and seminiferous tubular atrophy were newly observed, and decreased testis/epididymis weights, tubular vacuolation in the testes, and oligospermia and spermatic debris in the epididymides were still present. The male reproductive system toxicities were not reversible. The applicant explained that seminiferous tubular atrophy was likely naturally occurring because this finding was not observed at the end of a 28-day dosing period.

Based on the above, the NOAELs were determined to be 30 mg/kg in males and 100 mg/kg in females.

5.2.6 Four-week oral toxicity study in monkeys (CTD 4.2.3.2.10)

Rhesus monkeys (3/sex/group) were orally treated with letermovir 0 (vehicle), 10, 30, or 100 mg/kg for 4 weeks. Soft feces, liquid feces, salivation, body weight losses, and increased segmented neutrophils were observed at 100 mg/kg. Body weight losses tended to resolve by the end of the study in some animals, and there were no abnormalities in clinical chemistry or histopathological examination. Thus, the NOAEL was determined to be 100 mg/kg.

5.2.7 Thirteen-week oral toxicity study in monkeys (CTD 4.2.3.2.11)

Cynomolgus monkeys (4 or 6/sex/group) were orally treated with letermovir 0 (vehicle), 30, 100, or 300 mg/kg for 13 weeks. Due to the clinical signs of emesis, inappetence, soft/watery feces, decreased activity, and hunched posture in the 300 mg/kg group, the dose was reduced to 250 mg/kg on Day 11 (300/250 mg/kg group). A 4-week recovery period following the dosing period was scheduled for some animals. One of 12 animals in the 300/250 mg/kg group was euthanized in extremis on Day 21 due to severe aforementioned clinical signs despite the dose being lowered on Day 11 and a drug holiday starting on Day 18. The cause of the severe clinical signs was unknown. Soft/watery feces, inappetence, decreased activity, and emesis occurred also after the reduction of the dose in the 300/250 mg/kg group. All findings were reversible during the recovery period.

Based on the above, the NOAEL was determined to be 100 mg/kg.

5.2.8 Thirty-nine-week oral toxicity study in monkeys (CTD 4.2.3.2.12)

Cynomolgus monkeys (4 or 6/sex/group) were orally treated with letermovir 0 (vehicle), 25, 100, or 250 mg/kg for 39 weeks. Due to decreased body weight and body weight gain, dehydration, thin body, hunched position, and decreased activity observed in the 250 mg/kg group, the dose was reduced to 200 mg/kg at Week 9 (250/200 mg/kg group). A 6-week recovery period following the dosing period was scheduled for some animals. Decreased hemoglobin concentration and red blood cells at ≥25 mg/kg, salivation and vomiting immediately after dosing, and glycogen depletion in the liver at ≥100 mg/kg, and decreased body weight gain and cholesterol, tubular vacuolation and nephropathy in the kidney, and thymic atrophy, which was considered secondary to stress, at 250/200 mg/kg were observed. The clinical signs mostly subsided following the reduction of the dose in the 250/200 mg/kg group. However, 2 of the 12 animals were taken off treatment at Week 20 or 37 due to body weight loss, resistance to dose administration, etc., and allowed to recover for 6 or 9 weeks, and their clinical signs subsided after the recovery period. The applicant explained that since the

changes in hematological and clinical chemistry parameters at ≤100 mg/kg were small without associated histopathological changes, the pathological finding in the liver was minimal, and the pathological findings in the kidney at 250/200 mg/kg were noted in only 1 animal and were slight, etc., these findings are of little toxicological significance. All findings were reversible after a recovery period.

Based on the above, the NOAEL was determined to be 100 mg/kg.

5.2.9 Twenty-eight-day intravenous toxicity study in monkeys (CTD 4.2.3.2.14)

Cynomolgus monkeys (3 or 5/sex/group) were intravenously treated with letermovir 0 (vehicle, 30% w/v HP-β-CD in a 5% glucose solution), 10, 30, or 100 mg/kg for 28 days. A 2-week recovery period following the dosing period was scheduled for some animals.

As systemic effects, there was an increase in testis/epididymis weights, adjusted to overall body weight, at ≥10 mg/kg. The applicant explained that this change is of unknown toxicological significance because the increase was not dose-related or associated with histopathological findings. As local effects, phlebitis, periphlebitis, myositis, and hemorrhage at the injection sites were observed in the vehicle and letermovir 10 and 30 mg/kg groups, and their severity was similar among these groups, suggesting minor irritancy due to vehicle. The severity of myositis at the injection sites was increased in the 100 mg/kg group compared to the vehicle group. All findings were reversible following a recovery period.

Based on the above, the NOAEL for systemic toxicity was determined to be 100 mg/kg, and the NOAEL for local toxicity was determined to be 30 mg/kg.

5.3 Genotoxicity (CTD 4.2.3.3.1.2, 4.2.3.3.1.4, 4.2.3.3.2.1)

A bacterial reverse mutation test (Ames test), a chromosomal aberration test in Chinese hamster V79 cells, and a mouse bone marrow micronucleus test (vehicle, 0.5% aqueous Cremophor) were performed. All genotoxicity studies of letermovir were negative, and it was concluded that letermovir has no genotoxic potential.

5.4 Carcinogenicity

Carcinogenicity studies were not conducted, given that the clinical use of letermovir is less than 6 months in duration and that there were no findings indicative of carcinogenicity such as proliferative lesions, in repeated-dose toxicity studies.

5.5 Reproductive and developmental toxicity

Fertility studies in rats and monkeys, embryo-fetal developmental toxicity studies in rats and rabbits, a rat study for effects on pre- and postnatal development, including maternal function, and a toxicity study in juvenile rats were conducted.

Letermovir-related skeletal malformations and variations, etc. were observed in rat and rabbit embryos/fetuses. The NOAEL for embryo-fetal developmental toxicity was determined to be 50 mg/kg in rats, and the $AUC_{0\text{-}24}$

at the NOAEL (259 μg·h/mL) was 2.6- or 4.3-fold the AUC_{0-24} at the recommended clinical IV or oral dose in HSCT recipients, respectively (100 or 60.8 μg·h/mL, respectively).[37)]

Letermovir placental transfer and lacteal secretion were demonstrated in rats [see Section 4.2.3 and Section 4.4.2].

5.5.1 Fertility and early embryonic development in rats after oral administration (CTD 4.2.3.5.1.2)

Wistar rats (24/sex/group) were orally treated with letermovir 0 (vehicle), 15, 60, or 240 mg/kg. Males were treated for 10 weeks prior to mating, throughout mating, and up to necropsy for a total of approximately 15 weeks, and females were treated for 2 weeks prior to mating, throughout mating, and up to gestation day 7 for a total of approximately 6 weeks. As clinical signs in males, decreases in food consumption and body weight gain, etc. during the dosing period were observed at 240 mg/kg. As effects on fertility and early embryonic development, decreased testis weight, seminiferous tubular degeneration, spermatic debris and oligospermia in the epididymis, an increase in the percentage of abnormal sperm, and decreased sperm count and motility in males and decreased fertility index, an increase in the mean pre-implantation loss, and decreases in the mean number of implantation sites and the number of viable embryos in females were observed at 240 mg/kg. The applicant explained that these changes observed in females are considered secondary to the changes in male sperm and reproductive organs.

Based on the above, the NOAEL for male general toxicity and fertility was determined to be 60 mg/kg, and the NOAEL for female general toxicity and fertility and early embryonic development was determined to be 240 mg/kg.

5.5.2 Fertility and early embryonic development in male rats after oral administration (CTD 4.2.3.5.1.3)

Male Wistar rats (44/group) were orally treated with letermovir 0 (vehicle), 30, 60, or 180 mg/kg for 15 weeks prior to mating, throughout mating, and up to necropsy for a total of approximately 19 weeks. Males were mated with untreated females following treatment. A 15-week recovery period following the dosing period was scheduled for some males, and these recovery males were subsequently mated with untreated females. As clinical signs, decreases in food consumption and the mean body weight gain, etc., were observed at 180 mg/kg. As effects on fertility, at 180 mg/kg, decreased plasma inhibin B concentrations, tubular atrophy, tubular cell vacuolation, germinal epithelial cell exfoliation, and increased multinucleate cells in the testes, oligospermia, spermatic debris, etc. in the epididymis, an increase in the percentage of abnormal sperm, and decreased sperm count and motility were observed, and increased pre-implantation loss was noted in mated females, which was considered secondary to the changes in sperm and male reproductive organs. Electron microscopy revealed intracytoplasmic and intercellular vacuoles in or between Sertoli cells due to dilatation of rough endoplasmic reticulum, indicating an impairment or loss of functional blood-testis barrier associated with the destruction of inter-Sertoli cell junctional complexes. The effects on Sertoli cells are considered correlated with a marked decrease in plasma inhibin B[38)] concentrations observed at 180 mg/kg.

[38)] Produced by Sertoli cells.

Decreased testis and epididymis weights, tubular atrophy and tubular cell vacuolation in the testes, oligospermia in the epididymis, abnormalities in spermatological parameters, decreased plasma inhibin B concentrations, and increased post-implantation loss were present after the recovery period, and the male reproductive organ toxicities were not reversible.

Based on the above, the NOAEL for male fertility was determined to be 60 mg/kg.

5.5.3 Fertility in male rats after oral administration (CTD 4.2.3.5.1.4)

Male Wistar Hannover rats (22/group) were orally treated with letermovir 0 [vehicle, 0.5% (w/v) methyl hydroxyethyl cellulose in deionized water], 30, 60, or 180 mg/kg for 15 weeks prior to mating, throughout mating, and up to the day before necropsy for a total of approximately 17 weeks. Males were mated with untreated females following treatment. As clinical signs, decreases in the mean food consumption and body weight gain were observed at 180 mg/kg. As effects on fertility, decreased testis weight, small testis, small epididymis, seminiferous tubule degeneration in the testes, oligospermia and cellular debris in the epididymis, decreased sperm concentration and motility, decreased male fecundity index (pregnant females/mated females), and decreased fertility index in mated females (pregnant females/females cohabited) were observed at 180 mg/kg.

Based on the above, the NOAEL for male general toxicity and fertility was determined to be 60 mg/kg.

5.5.4 Fertility in male monkeys after thirteen-week oral administration (CTD 4.2.3.5.1.5)

Male cynomolgus monkeys (6/group) were orally treated with letermovir 0 (vehicle), 60, 120, or 240 mg/kg for 13 weeks. An 8-week recovery period following the dosing period was scheduled for some animals. As clinical signs, salivation around the time of dosing[39)] at ≥60 mg/kg, and soft and watery feces at ≥120 mg/kg were observed. The applicant explained that these clinical signs are considered of little toxicological significance because there were no effects on other observations/examinations. In order to evaluate effects on fertility, semen analysis, flow cytometric analysis of testicular tissue, testicular size, blood hormone concentrations (testosterone, inhibin B, and follicle stimulating hormone), organ weights, and gross pathology of the male reproductive system and histopathology including spermatogenesis staging were assessed. As a result, there were no letermovir-related changes.

Based on the above, the NOAEL for male fertility was determined to be 240 mg/kg.

5.5.5 Embryo-fetal development in rats after oral administration (CTD 4.2.3.5.2.3)

Pregnant Wistar rats (22/group) were orally treated with letermovir 0 (vehicle), 10, 50, or 250 mg/kg from gestation day 6 through 17.

As clinical signs in dams, reddish vaginal discharge at ≥50 mg/kg, and salivation, piloerection, light-colored feces, soft feces, cold body surface, high-stepping gait, reduced amount of feces associated with decreased

39) The applicant explained that salivation was likely due to taste aversion.

food consumption, increased water consumption and urination, decreases in body weight and the mean body weight gain, small spleen, black spots in the gastric mucosa, empty small intestines, black/brown cecum contents, enlarged adrenals, and decreased placental weights at 250 mg/kg were observed. As embryo-fetal effects, decreased fetal weights with retarded ossification, increased incidences of skeletal malformations (supernumerary lumbar vertebrae, pelvic shift, missing head of 1st rib), skeletal variations (additional 14th ribs, altered shape of sacral vertebral arches), shortened umbilical cord, and edematous fetuses were observed at 250 mg/kg. On the other hand, the applicant explained that fetal eye malformations observed at ≥10 mg/kg and multiple fetal cardiovascular malformations observed at 250 mg/kg are unlikely to be related to letermovir because the incidences were within the historical control ranges of the laboratory. The applicant explained that reddish vaginal discharge noted in dams at ≥50 mg/kg was due to overflow of blood from the uterine to the vagina associated with cyclic endometrial changes during gestation and increased uteroplacental blood flow around gestation day 15, that this finding is generally observed during gestation (*Anat Rec.* 1939;74:273-95), and that no associated post-implantation loss was observed.

Based on the above, the NOAEL for both maternal general toxicity and embryo-fetal developmental toxicity was determined to be 50 mg/kg.

5.5.6 Embryo-fetal development in rabbits after oral administration (CTD 4.2.3.5.2.8)

Pregnant Himalayan rabbits (20/group) were orally treated with letermovir 0 (vehicle), 25, 75, or 225 mg/kg from gestation day 6 through 20. As clinical signs in dams, decreases in body weight, food consumption, and water consumption, adverse clinical signs such as discolored urine (green) (moribund condition) resulting in the euthanasia in 1 of the 20 animals, spontaneous abortions due to adverse clinical signs in 3 of the 20 animals, decreased absolute body weight gain in animals with viable fetuses, gaseous/hardened contents in the cecum or large intestine, hardened liver, and dilated/tightly-filled gall bladder were observed at 225 mg/kg. As embryo-fetal effects, total resorption, increased post-implantation loss, skeletal malformations (1 supernumerary presacral vertebra with 13th ribs), and increased incidence of skeletal variations (13th ribs [floating and comma-shaped or present fully]) were noted at 225 mg/kg.

Based on the above, the NOAEL for both maternal general toxicity and embryo-fetal developmental toxicity was determined to be 75 mg/kg.

5.5.7 Pre- and postnatal development, including maternal function in rats after oral administration (CTD 4.2.3.5.3.1)

Pregnant Wistar Hannover rats (24/group) were orally treated with letermovir 0 (vehicle), 10, 45, or 180 mg/kg from gestation day 6 to postpartum day 22. In dams, decreased body weight on the first day of dosing and increased total litter loss were observed at 180 mg/kg. In the F_1 generation, decreased body weight gain from postnatal day 1 to postnatal day 21, in males from postnatal week 12 to postnatal week 16, and in females from gestation day 0 to gestation day 3 and delayed vaginal opening (the mean age) were observed at 180 mg/kg. The applicant explained that these findings are considered of little toxicological significance because the reproductive performance was unaffected. There were no letermovir-related effects on

neurological development, reproductive performance, fertility, or other physical development parameters, and no histopathological findings in the testes were observed.

Based on the above, the NOAEL for maternal general toxicity was determined to be 45 mg/kg, and the NOAEL for the F_1 offspring was determined to be 180 mg/kg.

5.5.8 Two-week oral toxicity study in juvenile rats (CTD 4.2.3.5.4.1)

Male Wistar Hannover rats (5/group) (14 days of age) were orally treated with letermovir 0 (vehicle), 60, or 180 mg/kg for 2 weeks, and there were no letermovir-related findings, including pathological changes in the male reproductive organs.

Based on the above, the NOAEL was determined to be 180 mg/kg.

5.6 Local tolerance (CTD 4.2.3.6.4, 4.2.3.6.5)

Two local tolerance studies were conducted.

Single doses of vehicle (water for injection) or letermovir 5 mg/mL were administered intravenously, subcutaneously, intramuscularly, or intra-arterially to New Zealand White rabbits (24 males).[40)] The animals were treated in a left/right comparison (letermovir/vehicle). At 24 hours post-dose, letermovir-induced slight local intolerability, such as edema and erythema, in the intravenous, intramuscular, and intra-arterial groups, but no findings indicative of local intolerance were observed in the subcutaneous group. At 96 hours post-dose, the abnormal findings at the injection sites tended to be reversible across all routes of administration.

Single doses of vehicle (20% [w/v] cyclodextrin solution) or letermovir 2.5 or 5.0 mg/mL were administered intravenously, subcutaneously, intramuscularly, or intra-arterially to New Zealand White rabbits (24 males).[41)] The animals were treated in a left/right comparison (letermovir/vehicle). Following intravenous infusion, intra-arterial or subcutaneous injections of letermovir 2.5 or 5.0 mg/mL, no signs of local intolerability were observed. After intramuscular injection of either 2.5 or 5.0 mg/mL letermovir, focal necrosis of muscle cells with lymphocytic and histiocytic infiltration was observed at 24 hours post-dose, and the severity of these findings increased concentration-dependently. In addition, intermuscular edema was seen at 24 hours after administration of 5.0 mg/mL letermovir. At 96 hours post-dose, the abnormal findings at the injection sites tended to be reversible at either concentration of letermovir.

The applicant's explanation about the risk of local intolerance in clinical use of the IV formulation:
In clinical use, the letermovir concentration is approximately 0.2% (w/v), and injection site reactions were mild in severity and rare in clinical studies [see Section 7.R.3.3]. Thus, the risk of local intolerance is considered

40) Animals were divided into 4 groups by route of administration (6 animals each): (1) intravenous (bolus) and intramuscular administration, (2) intra-arterial (bolus) and subcutaneous administration, (3) intravenous administration (15-minute infusion), (4) intra-arterial administration (15-minute infusion).

41) Animals were divided into 4 groups by letermovir concentration and route of administration (6 animals each): (1) intravenous (15-minute infusion) and subcutaneous administration of 2.5 mg/mL, (2) intramuscular and intra-arterial administration of 2.5 mg/mL, (3) intravenous (15-minute infusion) and subcutaneous administration of 5.0 mg/mL (4) intramuscular and intra-arterial administration of 5.0 mg/mL.

low.

5.7 Other toxicity studies

5.7.1 Toxicity assessment of impurities

The general toxicity and genotoxicity of the enantiomer of letermovir present in the drug substance were assessed.

A 13-week repeated oral dose toxicity study was conducted in rats with a batch containing the enantiomer at a level not less than the specification limit ([redacted]%) [see Section 5.2.3]. When the human equivalent dose of the enantiomer determined from the NOAEL for letermovir established in this study (60 mg/kg) was compared to the dose of the enantiomer at the maximum clinical dose of letermovir, the safety margin was 1.2-fold. Based on genotoxicity studies with a batch containing the enantiomer at a level not less than the specification limit [see Section 5.3], it was concluded that the enantiomer has no genotoxic potential.

Based on the above, it was concluded that the enantiomer that is present at a level up to the upper specification limit in the drug product poses little safety concern.

5.7.2 Phototoxicity (CTD 4.2.3.7.7.3)

Since the molar extinction coefficient of letermovir at 290 nm is greater than the threshold for phototoxicity assessment (1000 L mol^{-1} cm^{-1}) as per "Guideline on Photosafety Evaluation of Pharmaceuticals" (PFSB/ELD Notification No. 0521-1 dated May 21, 2014), phototoxicity testing was conducted.

Female Long-Evans rats were orally treated with letermovir 0 (vehicle), 100, or 500 mg/kg QD for 3 days, and the skin and eyes of the rats were exposed to ultraviolet light (10 J/cm^2) at 4 hours after the last dose. There were no skin reactions indicative of phototoxicity, and ophthalmic examination and histopathological examination of the eyes revealed no abnormal findings.

The applicant explained that based on the above, letermovir is unlikely to be phototoxic.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, there is no particular problem with the clinical use of letermovir from a toxicological perspective.

5.R.1 Toxicological evaluation of intravenous letermovir

The repeated intravenous dose toxicity of letermovir was evaluated in 28-day studies in rats and monkeys only, and the reproductive and developmental toxicity of letermovir was evaluated in oral studies only. PMDA asked the applicant to explain the sufficiency of testing of chronic general toxicity and reproductive and developmental toxicity of intravenous letermovir.

The applicant's explanation:

In repeated oral dose toxicity studies in rats (up to 26 weeks) and monkeys (up to 39 weeks), and oral reproductive and developmental toxicity studies, the general toxicity or reproductive and developmental toxicity of letermovir was evaluated at exposures higher than the systemic exposure at the recommended clinical intravenous dose in HSCT recipients. Rat and monkey 28-day intravenous and 4-week oral toxicity studies showed similar systemic toxicity profiles of oral and intravenous letermovir. Thus, the safety of intravenously administered letermovir can be explained, taking also account of the results from oral toxicity studies.

PMDA accepted the applicant's explanation.

5.R.2 Embryo-fetal effects

PMDA asked the applicant to explain fetal skeletal malformations or variations observed in embryo-fetal developmental toxicity studies in rats and rabbits [see Section 5.5.6 and Section 5.5.7].

The applicant's explanation:
Though all of the fetal skeletal abnormalities observed in rats and rabbits occurred at dose levels exhibiting maternal toxicity, as letermovir crosses the placenta and distributes into the fetus [see Section 4.2.3], the possibility that these findings were attributed to the direct toxicity of letermovir cannot be ruled out. The systemic exposure (1095 μg·h/mL) at which embryo-fetal toxicities were observed in rats was 11- or 18-fold the $AUC_{0\text{-}24}$ at the recommended clinical intravenous or oral dose in HSCT recipients (100 or 60.8 μg·h/mL, respectively).[37)]

PMDA's view:
Given that letermovir-related fetal skeletal abnormalities etc. were observed in rats and rabbits, the use of letermovir in pregnant women or in women who may possibly be pregnant is discussed in the clinical section [see Section 7.R.3.4].

5.R.3 Testicular effects

PMDA asked the applicant to explain testicular toxicities seen in toxicity studies in rats.

The applicant's explanation:
Although the mechanism of testicular toxicities observed in rats is unknown, the testicular effects appear to be similar to findings associated with Sertoli cell toxicity (*Toxicol Pathol*. 2001;29:64-76), taking account of their morphologic characteristics (clear, large, round vacuoles near the basal membrane of the seminiferous tubule that was affected slightly, and the retention of mature sperm and spermatic debris at the tip of the germinal epithelium in the seminiferous tubule). As testicular toxicity was not noted in mice or monkeys, testicular toxicity is considered rat-specific.

In a global phase III study in HSCT recipients (Study 001), serum inhibin B, luteinizing hormone, follicle

stimulating hormone, and testosterone levels were measured[42] at baseline, the end of study treatment (Week 14), and Week 24 post-transplant in male subjects treated with letermovir or placebo for 14 weeks (194 subjects in the letermovir group, 103 subjects in the placebo group) in order to assess the effects of letermovir on the testicular function. As a result, the changes from baseline in these values tended to be similar between the letermovir and placebo groups. In this study, male reproductive organ-related adverse events[43] were similar between the letermovir and placebo groups, and no serious events were reported.

Based on the above, testicular toxicity associated with letermovir is unlikely to occur in humans. However, the information on testicular toxicities observed in rats will be included in the package insert.

PMDA's view:
Although the detailed mechanism of testicular toxicities associated with letermovir observed in rats is unknown, similar findings were not observed in mice or cynomolgus monkeys. In the global phase III study (Study 001) in which letermovir was administered for 14 weeks, longer than the human spermatogenic cycle, there were no events indicative of testicular toxicity associated with letermovir. Based on these findings, the applicant's explanation (testicular toxicity is unlikely to become a safety concern in humans treated with letermovir at the proposed dosing regimen) is acceptable.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

In the clinical development of the oral formulation, 4 different formulations containing letermovir (PMF1 formulation [a film-coated tablet], PMF2 formulation [a film-coated tablet that differed from PMF1 formulation in [redacted] and the specification for an excipient, [redacted]], PMF3 formulation [a film-coated tablet that differed from PMF2 formulation in [redacted], the specification for [redacted], and [redacted] of [redacted]], FMI formulation [a film-coated tablet that differed from PMF3 formulation in the addition of [redacted]]) were mainly used.[44] PMF1, PMF2, PMF3, and FMI formulations differed in [redacted], and grade or [redacted] of [redacted], but were similar with respect to [redacted] of [redacted] and [redacted]. Thus, the similarity of the formulations was assessed by dissolution testing.

[42] The applicant's explanation: Study 001 enrolled HSCT recipients, and taking also into account that they used immunosuppressants etc. which may affect male reproductive function, and that their general condition was not good, and considering a burden on patients, semen analysis was not performed, and serum inhibin B, luteinizing hormone, follicle stimulating hormone, and testosterone levels were measured as surrogate markers for testicular function.
These markers are listed as biomarkers of testicular injury in a draft guidance on testicular toxicity and evaluation during drug development (Testicular Toxicity Evaluation during Drug Development Guidance for Industry DRAFT GUIDANCE; July 2015) released by the US FDA.

[43] Defined as events coded to MedDRA/J ver.19 System Organ Class (SOC) "Reproductive system and breast disorders." Adverse events occurring in male subjects during the study treatment period were balanoposthitis, erectile dysfunction, genital erythema, genital ulceration, penile burning sensation, penile pain, scrotal erythema, scrotal irritation, scrotal pain, and testicular pain, and the incidences of individual events were similar between the letermovir and placebo groups, i.e. 0% to 0.5%.

[44] PMF1 formulation was used in phase I studies (Studies P014, P015, P016, P017, P018, P022, P025, P026, and P027) and a phase II study (Study P020). PMF2 formulation was used in a phase I study (Study P006). PMF3 formulation was used in phase I studies (Studies P023, P029, P028, P032, P033, P034, and P035) and a phase III study (Study P001). FMI formulation was used in phase I studies (Studies P003 and P036) and the phase III study (Study P001).

Dissolution testing of PMF1 and PMF3 formulations[45)] and dissolution testing of PMF3 and FMI formulations[46)] demonstrated the comparability of dissolution profiles of the respective two formulations. PMF3 and FMI formulations were used in a global phase III study (Study 001), and the commercial formulation in Japan is identical to FMI formulation except for the debossed marking.

In the clinical development of the IV formulation, an aqueous solution containing HP-β-CD as a solubilizer for intravenous infusion was mainly used.[47)] This formulation is identical to the commercial formulation in Japan, except for container closure system.

This section describes the results from the main biopharmaceutic studies (absolute bioavailability, relative bioavailability, and food effect studies). Letermovir concentrations in human plasma and urine were determined by liquid chromatography/tandem mass spectrometry (LLOQ, 0.10-10.0 ng/mL in plasma, 1.00-10 ng/mL in urine). Unless otherwise specified, PK parameters are expressed as the geometric mean.

6.1.1 Absolute bioavailability study (Reference data, CTD 5.3.1.1.2, Study 017 [20 to 20])

A 2-treatment, 2-period, crossover study was conducted in non-Japanese healthy women (12 subjects included in PK assessment) to investigate the PK of letermovir after a single oral dose of 30 mg of letermovir (PMF1 formulation) or a single intravenous dose of 30 mg of letermovir (infused over 30 minutes). The absolute bioavailability of letermovir [90% confidence interval (CI)], based on the geometric least-squares mean ratio of AUC_{last}, was 75.8 [68.4, 84.0]%.

6.1.2 Relative bioavailability study (Reference data, CTD 5.3.1.2.2, Study 028 [20 to 20])

A 2-treatment, 2-period, crossover study was conducted in non-Japanese healthy women (14 subjects included in PK assessment) to compare the PK of letermovir after a single dose administration of 1 × 480-mg tablet vs. 2 × 240-mg tablets (all PMF3 formulations) under fasted conditions. The results are shown in Table 16. The geometric least-squares mean ratios of C_{max} and AUC_{last} (1 × 480-mg tablet/2 × 240-mg tablets) [90% CI] were 1.07 [0.95, 1.21] and 1.10 [1.02, 1.18], respectively.

Table 16. PK parameters after a single dose administration of 1 × 480-mg tablet vs. 2 × 240-mg tablets

	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	t_{max} (h)[a)]	$t_{1/2}$ (h)
480-mg tablet (1 tablet)	14	11.9 (35.6)	83.6 (33.8)	3.00 [2.00, 4.00]	11.0 (42.6)
240-mg tablet (2 tablets)	14	11.1 (45.4)	76.1 (32.6)	3.00 [2.00, 5.00]	11.7 (41.8)

Geometric mean (CV%)
a) Median [Range]

6.1.3 Food effect study (CTD 5.3.1.1.3, Study 029 [20])

A 2-treatment, 2-period, crossover study was conducted in non-Japanese healthy women (14 subjects included in PK assessment) to evaluate the effect of food on the PK of letermovir. Subjects received a single oral dose

45) Dissolution test was performed according to the Paddle Method (50 revolutions/min plus 100 revolutions/min for pH) using dissolution media (pH 1.2, , 6.8, and water).

46) Dissolution test was performed in accordance with the specification (37 ± 0.5°C, the Paddle Method, revolutions/min, mmol/L buffer added with % [w/v] , pH).

47) In non-clinical studies and early clinical studies (Studies 017 and 018), a formulation containing as a solubilizer was used. However, as subjects who received this formulation had mild to moderate injection site irritation and thrombophlebitis, a formulation containing HP-β-CD as a solubilizer was used in subsequent clinical studies.

of 1 letermovir 480-mg tablet (PMF3 formulation) under fasted conditions or at 30 minutes after the start of a high-fat meal (approximately 920 kcal, 58.4 g fat). The results are shown in Table 17. The geometric least-squares mean ratios of C_{max} and AUC_{last} (fed/fasted) [90% CI] were 1.30 [1.04, 1.62] and 1.00 [0.84, 1.18], respectively.

The applicant's explanation:
The AUC_{last} of letermovir was similar under fasted or fed conditions, and the food effect is not clinically relevant.

The difference between the to-be-marketed formulation in Japan (FMI 240-mg tablet formulation) and PMF3 240-mg tablet formulation is the presence or absence of [redacted] only, the comparability of dissolution profiles of the 2 formulations has been demonstrated, and the PK of letermovir from PMF3 480-mg tablet formulation were similar to those from PMF3 240-mg tablet formulation [see Section 6.1.2]. Thus, the effect of food with the to-be-marketed formulation in Japan can be assessed using the data from Study 029.

Table 17. PK parameters of letermovir under fasted or fed conditions

Presence or absence of food	N	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	t_{max} (h)[a)]	Geometric least-squares mean ratio (Fed/Fasted) [90% CI]	
					C_{max}	AUC_{last}
Fasted	14	11.8 (62.6)	85.9 (44.3)	2.76 [2.00, 5.00]	1.30 [1.04, 1.62]	1.00 [0.84, 1.18]
Fed	13	15.0 (20.9)	84.1 (19.2)	2.50 [1.50, 5.00]		

Geometric mean (CV%)
a) Median [Range]

6.2 Clinical pharmacology

The applicant submitted the results from studies in healthy subjects, HSCT recipients, and subjects with hepatic or renal impairment, the results from pharmacokinetic interaction studies, and the results of physiologically-based pharmacokinetic (PBPK) model analysis and PPK analyses with this application. *In vitro* studies using human biomaterials are described in the section of non-clinical pharmacokinetics [see Sections 4.2 to 4.5]. Unless otherwise specified, PK parameters are expressed as the geometric mean.

6.2.1 Studies in healthy subjects

6.2.1.1 Phase I study (CTD 5.3.3.1.1, Study 027 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of letermovir in plasma were investigated in Japanese healthy women (6 subjects per dose group included in PK assessment) following single oral doses of 240 to 720 mg of letermovir or single intravenous doses of 240 to 960 mg of letermovir (infused over 60 minutes).[48)] The results are shown in Table 18. The observed adverse events were all mild in severity, regardless of route of administration and dose level, and there were no adverse events leading to death, discontinuations, or serious adverse events.

48) This was a placebo-controlled, single ascending dose study. The safety, tolerability, and pharmacokinetics of letermovir were evaluated following single oral doses in Part 1 and single IV doses in Part 2.

Table 18. PK parameters following single oral or intravenous doses of letermovir

Route of administration	Dose (mg)	N	C_{max} (μg/mL)[a)]	AUC_{inf} (μg·h/mL)	t_{max} (h)[b)]	$t_{1/2}$ (h)	CL/F or CL (L/h)	V_z/F or V_z (L)
Oral	240	6	10.8 (26.6)	61.8 (43.1)	2.25 [1.00, 3.00]	9.96 (23.5)	3.88 (43.1)	55.8 (63.8)
	480	6	19.6 (30.0)	180 (35.1)	3.00 [3.00, 5.00]	9.66 (37.2)	2.67 (35.1)	37.3 (72.8)
	720	6	30.6 (30.8)	303 (52.9)	4.00 [2.50, 8.00]	13.3 (49.9)	2.38 (52.9)	45.8 (103.1)
IV	240	6	18.7 (16.2)	60.8 (20.2)	—	11.8 (64.0)	3.95 (20.2)	67.2 (75.6)
	480	6	41.0 (21.3)	176 (31.9)	—	10.8 (33.7)	2.73 (31.9)	42.5 (62.8)
	960	6	80.3 (15.6)	500 (31.6)	—	12.4 (49.3)	1.92 (31.6)	34.2 (61.5)

Geometric mean (CV%) —: Not applicable
CL/F: apparent clearance, V_z: volume of distribution during the terminal phase, V_z/F: apparent volume of distribution during the terminal phase
a) Concentration at the end of infusion (IV), b) Median [Range]

6.2.1.2 Phase I study (CTD 5.3.3.1.2, Study 032 [[redacted] to [redacted]])

The PK of letermovir were investigated in Japanese healthy women (14 subjects included in PK assessment) after oral administration of letermovir. The study consisted of Period 1 and Period 2. In Period 1, subjects received 480 mg letermovir orally QD for 7 days. In Period 2, subjects received 240 mg letermovir orally QD for 8 days plus a single dose of cyclosporine 200 mg on Day 8. The results are shown in Table 19. The accumulation ratios (Day 7/Day 1) based on $AUC_{0\text{-}24}$ and C_{max} following multiple doses of 480 mg QD for 7 days were 0.97 and 0.94, respectively. The geometric mean ratios of $AUC_{0\text{-}24}$ and C_{max} of letermovir (letermovir 240 mg QD for 8 days with/without cyclosporine) were 2.11 and 1.48, respectively. The observed adverse events were all mild or moderate in severity, regardless of route of administration and dose level, and there were no adverse events leading to death, discontinuations, or serious adverse events.

Table 19. PK parameters following multiple oral doses of letermovir

Regimen	N	Time point	C_{max} (μg/mL)	$AUC_{0\text{-}24}$ (μg·h/mL)	t_{max} (h)[a)]	$t_{1/2}$ (h)
Letermovir 480 mg QD	12	Day 1	22.0 (40.0)	141 (43.9)	2.50 [2.00, 3.00]	4.91 (16.9)
	12	Day 7	20.8 (48.7)	137 (55.0)	2.25 [2.00, 5.00]	10.5 (60.2)
Letermovir 240 mg QD (concomitant cyclosporine 200 mg on Day 8 only)	13	Day 1	8.51 (26.9)	40.0 (31.0)	2.00 [1.00, 5.00]	5.10 (12.1)
	12	Day 7	9.68 (30.4)	49.9 (32.9)	2.00 [1.00, 3.00]	5.74 (20.3)
	12	Day 8	14.3 (20.3)	105 (26.8)	2.02 [1.03, 3.00]	4.81 (16.3)

Geometric mean (CV%)
a) Median [Range]

6.2.1.3 Phase I study (Reference data, CTD 5.3.3.1.13, Study 005 [[redacted] to [redacted]])

The PK of letermovir were investigated in non-Japanese healthy women (the number of subjects included in PK assessment, 30 in Part A and 8 in Part B) following single or multiple IV doses of letermovir. This study consisted of 2 Parts. In Part A, subjects received a single IV infusion of letermovir in the range of 120 to 960 mg over 30 minutes (120 and 240 mg) or 60 minutes (480, 720, and 960 mg). In Part B, subjects received a single IV dose of letermovir 240 mg or letermovir 240 mg IV QD for 7 days (infused over 30 minutes). The results are shown in Table 20. Steady-state was reached by Day 5 after multiple dosing, and the accumulation ratios based on the C_{max} and $AUC_{0\text{-}24}$ of letermovir on Day 7 (Day 7 of multiple dosing/single dose administration) were 1.03 and 1.18, respectively.

Table 20. PK parameters following single or multiple IV doses of letermovir

Part	Regimen	Dose (mg)	N	C_{max} (μg/mL)[a)]	AUC (μg·h/mL)[b)]	$t_{1/2}$ (h)	CL (L/h)	V_d (L)
A	Single dose	120	6	7.33 (19.7)	13.2 (29.3)	11.6 (34.7)	9.10 (29.3)	152 (33.2)
		240	6	15.4 (21.7)	31.3 (31.1)	10.7 (16.3)	7.66 (31.1)	118 (37.6)
		480	6	27.0 (15.8)	104 (20.9)	12.6 (30.2)	4.62 (20.9)	83.8 (30.5)
		720	6	39.0 (7.90)	166 (13.5)	11.0 (35.6)	4.33 (13.5)	68.7 (44.4)
		960	6	56.8 (13.2)	244 (25.4)	12.3 (34.3)	3.94 (25.4)	70.1 (58.0)
B	Single dose	240	8	14.7 (8.24)	27.1 (17.3)	15.7 (39.1)	8.09 (19.7)	184 (34.8)

	Multiple doses (7 days)	240 QD	5	15.8 (13.0)	33.1 (19.2)	22.4 (84.9)	7.25 (19.2)	55.9 (45.6)

Geometric mean (CV%)
a) Concentration at the end of infusion, b) AUC_{inf} for single dose data, AUC_{0-24} for multiple dose data

6.2.1.4 Phase I study (Reference data, CTD 5.3.3.1.12, Study 026 [[redacted] to [redacted]])

The PK of letermovir were investigated in non-Japanese healthy women (the number of subjects included in PK assessment, 18 for oral administration and 9 for intravenous administration) following multiple oral doses of 720 mg letermovir BID for 14 days or multiple IV doses (infused over 60 minutes) of 480 mg letermovir QD for 7 days. The results are shown in Table 21. When subjects received 720 mg letermovir orally BID for 14 days, steady-state was reached by Day 9, and the accumulation ratios based on the AUC_{0-12}, C_{max}, and C_{12} of letermovir on Day 14 (Day 14/Day 1) were 1.50, 1.44, and 1.08, respectively. When subjects received 480 mg letermovir IV QD for 7 days, steady-state was reached by Day 4, and the accumulation ratios based on the AUC_{0-24}, C_{max}, and C_{24} of letermovir on Day 7 (Day 7/Day 1) were 1.22, 1.06, and 2.46, respectively.

Table 21. PK parameters following multiple oral or intravenous doses of letermovir

Regimen		N	Time point	C_{max} (μg/mL)[a)]	AUC (μg·h/mL)[b)]	C_{12} or C_{24} (μg/mL)[c)]	t_{max} (h)[d)]
Oral	720 mg BID	18	Day 1	18.6 (30.1)	111 (36.8)	3.57 (82.0)	3.00 [2.02, 5.03]
		17	Day 14	26.7 (32.1)	164 (44.8)	3.80 (102)	3.00 [2.00, 5.02]
IV	480 mg QD	9	Day 1	26.8 (12.6)	101 (28.8)	0.44 (67.4)	–
		9	Day 7	28.4 (14.4)	123 (30.9)	1.08 (56.2)	–

Geometric mean (CV%)
a) Concentration at the end of infusion (IV), b) AUC_{0-12} after oral dosing, AUC_{0-24} after IV dosing, c) C_{12} after oral dosing, C_{24} after IV dosing, d) Median [Range]

6.2.1.5 Mass balance study (Reference data, CTD 5.3.3.1.7, Study 021, Part 3 [[redacted] to [redacted]])

The mass balance of letermovir was evaluated in non-Japanese healthy men (8 subjects included in PK assessment). Subjects received oral unlabeled letermovir 80 mg BID for 4 days and unlabeled letermovir 80 mg that contains ^{14}C-letermovir on Day 5. The mean cumulative percentages of the radioactive dose recovered in urine and feces over 336 hours were 1.43% and 93.3%, respectively. During 0 to 24 hours post-dose, 84.1% of total radioactivity in plasma was recovered, and the majority was attributed to unchanged letermovir (96.6% of total radioactivity). Within 24 to 96 hours post-dose, 97.3% of total radioactivity in feces was recovered, and unchanged letermovir (70.5% of the administered dose), a metabolite, M7 (acyl-glucuronide, 6.0% of the administered dose), and uncharacterized metabolites (16.8%) were detected.

6.2.2 Intrinsic factor PK studies

6.2.2.1 Study in subjects with hepatic impairment (Reference data, CTD 5.3.3.3.1, Study 015 [[redacted] to [redacted]])

The PK of letermovir were investigated in 16 non-Japanese female subjects with hepatic impairment (moderate [Child-Pugh Class B] and severe [Child-Pugh Class C], 8 subjects each) and 16 female subjects with normal hepatic function (8 subjects each matched for age, body mass index [BMI], and race with subjects with moderate or severe hepatic impairment). All subjects received oral letermovir (moderate, 60 mg; severe, 30 mg) QD for 8 days. The results are shown in Table 22.

The applicant's explanation:

Taking account of the results from Study 015, and the clinical bounds for letermovir exposure (AUC) (0.5- to 3.0-fold of exposure of the recommended clinical doses)[49] established based on exposure-response analyses using the data from a global phase III study (Study 001) [see Section 6.2.5.3] and the results from clinical studies including phase I studies, etc., the package insert will advise careful administration in patients with severe hepatic impairment.

Table 22. PK parameters following multiple oral doses of letermovir in subjects with hepatic impairment and subjects with normal hepatic function

Degree of hepatic impairment	Dose (mg)	N	Letermovir	C_{max} (μg/mL)	AUC_{0-24} (μg·h/mL)	$t_{1/2}$ (h)	Geometric least-squares mean ratio [90% CI] (Hepatic impairment/Normal hepatic function)	
							C_{max}	AUC_{0-24}
Normal	60	8	Total	1.17 (74.2)	6.41 (54.6)	13.9 (38.9)	—	—
			Unbound	0.011 (79.3)	0.060 (57.5)	—	—	—
Moderate		8	Total	1.61 (33.0)	10.2 (63.0)	12.89 (25.9)	1.37 [0.87, 2.12]	1.59 [0.98, 2.57]
			Unbound	0.017 (48.4)	0.11 (85.1)	—	1.56 [0.93, 2.63]	1.81 [1.03, 3.20]
Normal	30	8	Total	0.50 (22.4)	2.68 (21.6)	12.84 (44.5)	—	—
			Unbound	0.005 (32.8)	0.026 (25.0)	—	—	—
Severe		8	Total	1.17 (24.7)	10.3 (37.5)	18.66 (33.3)	2.34 [1.91, 2.88]	3.82 [2.94, 4.97]
			Unbound	0.016 (47.2)	0.14 (49.2)	—	3.29 [2.33, 4.63]	5.36 [3.86, 7.44]

Geometric mean (CV%) —: Not applicable

6.2.2.2 Study in subjects with renal impairment (Reference data, CTD 5.3.3.3.2, Study 006 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of letermovir were investigated in 16 non-Japanese subjects with renal impairment (moderate [eGFR, 30-59 mL/min/1.73 m^2] and severe [eGFR <30 mL/min/1.73 m^2, not on dialysis], 8 subjects each) and 8 subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2, subjects matched for gender, age, and BMI with subjects with moderate or severe renal impairment). All subjects received oral letermovir 120 mg QD for 8 days. The results are shown in Table 23.

The applicant's explanation:

Taking account of the results from Study 006, and the clinical bounds for letermovir exposure (AUC) (0.5-3.0)[49] established based on exposure-response analyses using the data from a global phase III study (Study 001) [see Section 6.2.5.3] and the results from clinical studies including phase I studies, etc., no dose adjustment is necessary for patients with renal impairment.

[49] The applicant's explanation about the established clinical bounds for letermovir exposure (AUC) (lower bound, 0.5; upper bound, 3.0):
Based on the results of an exposure-response analysis using the data from a foreign phase II study at lower doses, and given that letermovir C_{max} was not associated with any safety finding in clinical studies, the PK parameter that can be most closely associated with toxicity, AUC, was selected as a measure of clinically relevant change. Although the results of exposure-response analyses using the data from a global phase III study (Study 001) found no associations between AUC and efficacy/safety at the letermovir exposure (AUC) range obtained [see Section 6.2.5.3], based on the following considerations, the clinical bounds for letermovir exposure (AUC) were established as the range of the relative changes that are clinically irrelevant for the efficacy and safety of letermovir.
Lower bound: The results of PPK analysis including Study 001 showed that the lower bound of the 90% confidence interval for the predicted AUC (16.9 μg·h/mL) in HSCT recipients after oral administration of letermovir 480 mg (lowest exposures after administration of letermovir), was 0.5-fold the median (34.4 μg·h/mL) [see Section 6.2.5.2].
Upper bound: Exposures that demonstrated acceptable safety in phase I studies (AUC_{0-24}, 328 μg·h/mL after oral administration [calculated by doubling the AUC_{0-12} after oral doses of letermovir 720 mg BID (Study 026, see Section 6.2.1.4)] and AUC_{0-24}, 282 μg·h/mL after IV administration [Study 004, see Section 6.2.4]) were approximately 3-fold the predicted AUC in HSCT recipients after administration of letermovir, 100 μg·h/mL [see Section 6.2.5.2].

Table 23. PK parameters following multiple oral doses of letermovir in subjects with renal impairment and subjects with normal renal function

Degree of renal impairment	Dose (mg)	N	Letermovir	C_{max} (μg/mL)	AUC_{0-24} (μg·h/mL)	$t_{1/2}$ (h)	Geometric least-squares mean ratio [90% CI] (Renal impairment/Normal renal function)	
							C_{max}	AUC_{0-24}
Normal	120	8	Total	2.42 (45.2)	11.0 (28.4)	14.4 (57.7)	—	—
			Unbound	0.023 (44.8)	0.10 (34.1)	—	—	—
Moderate		8	Total	3.04 (42.7)	21.2 (40.1)	22.8 (55.5)	1.25 [0.87, 1.82]	1.92 [1.43, 2.58]
			Unbound	0.032 (39.4)	0.22 (36.8)	—	1.41 [0.98, 2.01]	2.15 [1.59, 2.91]
Severe		8	Total	2.57 (37.1)	15.7 (97.0)	19.7 (52.4)	1.06 [0.75, 1.51]	1.42 [0.83, 2.43]
			Unbound	0.030 (35.5)	0.19 (96.9)	—	1.35 [0.96, 1.90]	1.81 [1.04, 3.12]

Geometric mean (CV%)—: Not calculated or not applicable

6.2.3 Pharmacokinetic interaction studies[50)]

Twelve pharmacokinetic interaction studies of letermovir and other drugs were conducted. The geometric least-squares mean ratios of PK parameters of letermovir or coadministered drugs for coadministration vs. alone are shown in Table 24 and Table 25.

Table 24. Effect of co-administered drugs on PK parameters of letermovir

Co-administered drug	Regimen		N	Geometric least-squares mean ratio [90% CI] (with/without co-administered drug)	
	Co-administered drug	Letermovir		AUC[a)]	C_{max}
Cyclosporine	200 mg PO single dose	240 mg PO QD	12	2.11 [1.97, 2.26]	1.48 [1.33, 1.65]
Tacrolimus	5 mg PO single dose	80 mg PO BID	14	1.02 [0.97, 1.07]	0.92 [0.84, 1.00]
Mycophenolate mofetil	1 g PO single dose	480 mg PO QD	14	1.18 [1.04, 1.32]	1.11 [0.92, 1.34]

PO: oral
a) AUC: AUC_{0-24} ratio for letermovir QD, AUC_{0-12} ratio for letermovir BID

Table 25. Effect of letermovir on PK parameters of co-administered drugs

Drug	Regimen		N	Geometric least-squares mean ratio [90% CI] (with/without letermovir)	
	Co-administered drug	Letermovir		AUC_{inf}	C_{max}
Midazolam	1 mg IV single dose	240 mg PO QD	16	1.47 [1.37, 1.58]	1.05 [0.94, 1.17]
	2 mg PO single dose	240 mg PO QD	16	2.25 [2.04, 2.48][b)]	1.72 [1.55, 1.92]
Cyclosporine	50 mg PO single dose	240 mg PO QD	14	1.66 [1.51, 1.82]	1.08 [0.97, 1.19]
Tacrolimus	5 mg PO single dose	480 mg PO QD	14[a)]	2.42 [2.04, 2.88]	1.57 [1.32, 1.86]
Sirolimus	2 mg PO single dose	480 mg PO QD	14[a)]	3.40 [3.01, 3.85]	2.76 [2.48, 3.06]
Mycophenolate mofetil	1 g PO single dose	480 mg PO QD	14	1.08 [0.97, 1.20]	0.96 [0.82, 1.12]
Digoxin	0.5 mg PO single dose	240 mg PO BID	22	0.88 [0.80, 0.96][b)]	0.75 [0.63, 0.89]
Atorvastatin	20 mg PO single dose	480 mg PO QD	14[a)]	3.29 [2.84, 3.82]	2.17 [1.76, 2.67]
Acyclovir	400 mg PO single dose	480 mg PO QD	16[a)]	1.02 [0.87, 1.20]	0.82 [0.71, 0.93]
Voriconazole	200 mg PO BID	480 mg PO QD	14[c)]	0.56 [0.51, 0.62][d)]	0.61 [0.53, 0.71]
Posaconazole[e)]	300 mg PO single dose	480 mg PO QD	16[a)]	0.98 [0.82, 1.17]	1.11 [0.95, 1.29]
Ethinylestradiol[f)]	0.03 mg/0.15 mg PO single dose	480 mg PO QD	22	1.42 [1.32, 1.52]	0.89 [0.83, 0.96]
Levonorgestrel[f)]				1.36 [1.30, 1.43]	0.95 [0.86, 1.04]

PO: oral, IV: intravenous
a) Coadministration, N = 13, b) AUC_{last} ratio, c) Coadministration, N = 12, d) AUC_{0-12} ratio, e) Unapproved in Japan, f) Administered as ethinylestradiol/levonorgestrel combination product

6.2.4 QT/QTc study (CTD 5.3.4.1.1, Study 004 [[redacted] to [redacted]])

A 4-treatment, 4-period, crossover study was conducted in 38 non-Japanese healthy women to determine the effect of letermovir on the QTc interval. Moxifloxacin (a single oral dose of 400 mg) was used as a positive control, and subjects received a single IV infusion of placebo or letermovir 480 or 960 mg over 60 minutes.

50) Reference data, CTD 5.3.3.4.3, Study 003 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.4, Study 013 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.1, Study 016 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.1.11, Study 018, Part C [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.6, Study 022 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.10, Study 023 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.8, Study 025 [[redacted] to [redacted]]; CTD 5.3.3.1.2, Study 032 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.9, Study 033 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.7, Study 034 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.11, Study 035 [[redacted] to [redacted]]; Reference data, CTD 5.3.3.4.5, Study 036 [[redacted] to [redacted]].

The maximum mean difference in QTcP interval[51] change from baseline between moxifloxacin and placebo [90% CI] was 12.2 [10.7, 13.8] ms (at 4 hours post-dose). The maximum mean difference in QTcP interval change from baseline between letermovir 480 or 960 mg and placebo [90% CI] was 2.72 [1.05, 4.38] or 4.93 [2.81, 7.05] ms (at 1 hour post-dose), respectively. The applicant explained that the upper limit of the 90% confidence interval was below 10 ms, indicating no prolongation of QTc interval at doses up to 960 mg (IV administration). Following a single IV dose of letermovir 960 mg, the C_{max} and AUC_{0-24} were 67.3 μg/mL and 282 μg·h/mL, respectively.

6.2.5 PPK analyses and exposure-response analyses

6.2.5.1 PPK analysis using PK data from healthy subjects (Reference data, CTD 5.3.3.5.2)

Using letermovir PK data from healthy subjects in 12 phase I studies[52] (280 subjects, 9008 samples), PPK analysis (NONMEM version 7.3) was performed. The final model was a 4-compartment model with nonlinear CL and intercompartmental CL, autoinduction of CL, and first-order elimination. Oral absorption was described by a transit compartment absorption model. Potential covariates were evaluated. As a result, the effect of body weight on maximal CL and the effect of body weight and Asian race on V_d were selected as covariates.[53] At oral doses of 240 mg QD and 480 mg QD, CL increase (steady-state compared to baseline) was estimated at 20.1% and 17.1%, respectively. The absolute bioavailability of oral letermovir in healthy subjects [95% CI] was estimated at 93.8 [90.6, 97.4]%.

Concerning the effect of body weight, the predicted AUC was 18.7% lower in a Caucasian population with a mean body weight of 80 to 100 kg than in a Caucasian population with a mean body weight of 67.1 kg. The applicant explained that the exposure change is small and dose adjustment according to body weight is not required.

6.2.5.2 PPK analysis using PK data from healthy subjects and patients (Reference data, CTD 5.3.3.5.3)

Using letermovir PK data from healthy subjects or HSCT recipients in 3 phase I studies (Studies 022, 026, and 032), a foreign phase II study (Study 020), and a global phase III study (Study 001) (399 subjects, 2888 samples), PPK analysis (NONMEM version 7.3) was performed. The final model was a 2-compartment model with linear elimination and an absorption lag time.[54] Although the use of cyclosporine was included as a covariate, no covariates other than those selected in the PPK analysis in healthy subjects [see Section 6.2.5.1] were added because residual variability was inflated in further covariate exploration. The letermovir AUC_{0-24} values at steady-state following oral or intravenous administration of letermovir 480 mg or 240 mg with concomitant cyclosporine in HSCT recipients, predicted by simulations using the final model are shown in

[51] The appropriateness of Fridericia's and Bazett's formulae for QT interval correction was determined by a linear regression model, using QTc/RR data for the placebo and baseline study population (QT interval corrected for heart rate using Fridericia's formula [QTcF interval] or QT interval corrected for heart rate using Bazett's formula [QTcB interval] vs. RR interval on Holter ECG). The 95% confidence interval for the estimated slope of the linear regression did not include zero with either correction method, and both correction methods were considered inappropriate. In this study, the regression coefficient estimated in a linear regression model with the log-transformed RR interval vs. the log-transformed QT interval by treatment group as a covariate was used as a correction factor, and the corrected QT (QTc) interval was used for analysis (QTcP interval).

[52] Studies 005, 009, 014, 017, 018, 021, 022, 026, 027, 028, 029, and 032

[53] The effect of body weight, age, gender, race (White and others/Black/Asian), rs4149056 (OATP1B1/1B3), rs2306283 (OATP1B1/1B3), and UGT1A1*6 on CL and the effect of body weight, Asian race, age, gender, rs4149056 (OATP1B1/1B3), rs2306283 (OATP1B1/1B3), and UGT1A1*6 on V_d were evaluated as covariates.

[54] In a global phase III study (Study 001), subjects received letermovir 480 mg alone or 240 mg with concomitant cyclosporine, which is expected to provide a similar exposure as 480 mg alone, and letermovir PK samples were collected at steady-state only. Thus, the simplified model was used, compared to the PPK model in healthy subjects [see Section 6.2.5.1].

Table 26. The absolute bioavailability of letermovir after oral administration of letermovir 480 mg or coadministration of letermovir 240 mg and cyclosporine in HSCT recipients was estimated at approximately 35% or 85%, respectively, and the steady-state CL was estimated at 4.84 or 3.38 L/h, respectively.

Table 26. Letermovir PK parameters at steady state (predicted by simulations using the final model)

Dosing regimen	$AUC_{0\text{-}24}$ (μg·h/mL)	
	Oral	IV
Letermovir 480 mg QD	34.4 [16.9, 73.7]	100 [65.3, 148]
Letermovir 240 mg QD (with cyclosporine)	60.8 [28.7, 122]	70.3 [46.2, 106]

Median [90% prediction interval]

The applicant's explanation about differences in the absolute bioavailability of letermovir between healthy subjects [see Section 6.2.5.1] and HSCT recipients:

HSCT recipients received cancer chemotherapy or radiation therapy before transplantation, and gastrointestinal mucosal disorder is known as an adverse reaction to these therapies. It has been reported that gastrointestinal mucosal disorder induced by cancer chemotherapy etc. in HSCT recipients may reduce the gastrointestinal absorption of drugs such as cyclosporine, mycophenolate mofetil, and posaconazole, resulting in decreased plasma concentrations of these drugs (*Biol Blood Marrow Transplant*. 2003;9:304-11, *Eur J Drug Metab Pharmacokinet*. 2017;42:183-9, *Eur J Clin Pharmacol*. 2016;72:953-63). Thus, also in HSCT recipients treated with letermovir, gastrointestinal mucosal disorder induced by cancer chemotherapy etc. was likely to reduce the gastrointestinal absorption of letermovir.

6.2.5.3 Exposure-response analyses (Reference data, CTD 5.3.5.3.4)

Using the data from a global phase III study (Study 001), the association between the predicted $AUC_{0\text{-}24}$ at the recommended clinical dose in HSCT recipients[55)] and the primary endpoint (the proportion of patients with clinically significant CMV infection through Week 24 post-transplant) was assessed. As a result, at the exposure range obtained, no apparent association was found between the primary endpoint and letermovir exposure, and no clinically relevant covariate for the primary endpoint was identified.

The association between the predicted $AUC_{0\text{-}24}$ in HSCT recipients[55)] and clinically noteworthy adverse events (cardiac disorders, gastrointestinal disorders, acute renal failure, and ear and labyrinth disorders) was assessed. As a result, at the exposure range obtained, no associations were found between the incidences of these adverse events and letermovir exposure.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK of letermovir between Japan and overseas

The applicant's explanation about the PK of letermovir in Japanese and non-Japanese subjects:

Following a single dose of letermovir 480 mg in Japanese and non-Japanese healthy women, the geometric mean ratios of AUC_{inf} and C_{max} [90% CI] (Japanese/non-Japanese)[56)] were 2.53 [1.88, 3.39] and

55) Predicted exposures used for assessment of the relationship between letermovir exposure and the primary endpoint were calculated as weighted Bayesian estimates for dosing condition (concomitant use of cyclosporine and route of administration), accounting for the number of doses administered by each route during the treatment period. Exposures used for assessment of the relationship between letermovir exposure and clinically noteworthy adverse events were calculated as Bayesian estimates for dosing condition on the day of the adverse event.

56) Calculated by an analysis of variance (ANOVA) model with a factor of ethnic group, using PK parameters in Japanese subjects in Study 027 [see Section 6.2.1.1] and PK parameters in non-Japanese subjects in Studies 005 and 022.

1.52 [1.16, 1.98], respectively, after oral administration, and 1.69 [1.28, 2.23] and 1.51 [1.25, 1.84], respectively, after intravenous administration. Following multiple oral doses of letermovir 480 mg QD in Japanese and non-Japanese healthy women, the geometric mean ratios of AUC_{0-24} and C_{max} [90% CI] (Japanese/non-Japanese)[57] were 1.92 [1.40, 2.64] and 1.60 [1.22, 2.09], respectively, which showed a similar trend as that of a single dose administration.

Based on the results of PPK analysis including the data from a global phase III study (Study 001), predicted exposures in Japanese and non-Japanese HSCT recipients are shown in Table 27. The distribution of exposures largely overlapped between Japanese and non-Japanese patients.

Table 27. Steady-state PK parameters of letermovir by ethnic group (Bayesian estimates of the final model)

Regimen	Ethnic group	AUC_{0-24} (μg·h/mL)	
		Oral	IV
Letermovir 480 mg QD	Japanese	42.3 [28.3, 71.8]	100 [77.5, 171]
	Non-Japanese	34.3 [12.1, 94.3]	95.8 [72.0, 147]
Letermovir 240 mg QD (with cyclosporine)	Japanese	64.0 [55.7, 99.1]	70.9 [56.6, 90.2]
	Non-Japanese	60.2 [26.2, 115]	68.8 [40.0, 98.3]

Median [Range]

Since letermovir is a substrate of OATP1B1/3 and UGT1A1/3 [see Section 4.3.2 and Section 4.5.2], and polymorphisms of OATP1B1 and UGT1A1 have been reported to contribute to pharmacokinetic differences between Asians and Caucasians (*Clin Pharmacol Ther.* 2010;87:130-3, *Clin Pharmacol Ther.* 2013;94:37-51, *Clin Pharmacol Ther.* 2009;85:623-7), pharmacogenetic analyses were performed to evaluate the effects of these polymorphisms[58] on the PK of letermovir. In Asian and Caucasian subjects, the geometric mean ratios of AUC were 1.42 and 1.16, respectively, when heterozygous carriers of the recessive allele of the gene encoding OATP1B1 gene (rs4149056) (1 copy) were compared to non-carriers. In Asian and all subjects, the geometric mean ratios of AUC were 1.46 and 1.36, respectively, when heterozygous or homozygous carriers of the recessive allele of UGT1A1 gene (rs4148323) (≥1 copy) were compared to non-carriers. The effects of these polymorphisms were insignificant. Based on PPK analysis in healthy subjects, any of the polymorphisms did not have an effect on letermovir exposure.

Based on the above, although predicted letermovir exposures were higher in Japanese healthy subjects than in non-Japanese healthy subjects, the distribution of predicted letermovir exposures almost overlapped between Japanese and non-Japanese HSCT recipients, and the safety profile of letermovir in Japanese subjects was favorable in all clinical studies [see Section 6.2.1.1, Section 6.2.1.2, and Section 7.R.3.1]. For these reasons, the differences in letermovir exposure between Japanese and non-Japanese subjects are not clinically relevant.

PMDA accepted the applicant's explanation (although there is limited clinical experience with letermovir in Japanese subjects, the differences in letermovir exposure between Japanese and non-Japanese subjects are not clinically relevant based on comparison of exposures between Japanese and non-Japanese subjects and the safety profile in clinical studies, etc.).

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57) Calculated by an ANOVA model with a factor of ethnic group, using PK parameters in Japanese subjects in Study 032 [see Section 6.2.1.2] and PK parameters in non-Japanese subjects in Study 022.

58) Polymorphisms studied are as follows: OATP1B1, rs4149056, rs2306283, and rs4149032 single nucleotide polymorphisms (SNPs); UGT1A1, UGT1A1*6 (rs4148323) SNP and UGT1A1*28 (a TA repeat variant in the promotor)

6.R.2 Selection of dosing regimen for phase III study

The applicant's explanation about the rationale for the dosing regimen selected for a global phase III study (Study 001):

Based on the following points, the 480 mg QD regimen or the 240 mg QD regimen with concomitant cyclosporine was chosen for Study 001, for both the tablet and IV formulations. Since the effect of food after oral administration of letermovir was not considered clinically relevant [see Section 6.1.3], letermovir was administered without regard to food.

- The results of an exploratory exposure-response analysis using the data from a foreign phase II study in CMV-seropositive allo-HSCT recipients [Study 020, see Section 7.1] showed that only subjects with a steady-state letermovir $AUC_{0\text{-}24}$ <45 μg·h/mL developed CMV viremia or CMV disease. Simulations based on PPK analysis predicted that letermovir 480 mg orally QD achieves a steady-state $AUC_{0\text{-}24}$ ≥45 μg·h/mL in >90% of patients.
- Given that cyclosporine increased letermovir exposure in a pharmacokinetic interaction study of letermovir and cyclosporine, simulations based on PPK analysis were performed, which predicted that letermovir 240 mg with concomitant cyclosporine provides a similar exposure as letermovir 480 mg orally QD.
- The absolute bioavailability of oral letermovir was high in a phase I study in healthy subjects (Study 017) [see Section 6.1.1].
- Although letermovir exposure was higher in Japanese healthy subjects than in non-Japanese healthy subjects, the safety profile in Japanese healthy subjects was favorable [see Section 6.R.1].

Based on the following points etc., both letermovir 240 and 480 mg IV were infused over 60 minutes (the final solution for infusion, 250 mL) in Study 001.

- In phase I studies [Studies 004 and 005, see Section 6.2.4 and Section 6.2.1.3], the infusion time was 30 or 60 minutes, according to the volume of the final solution for infusion (150 or 300 mL, respectively), and the safety and tolerability of letermovir at concentrations up to 3.2 mg/mL administered as a single intravenous infusion were demonstrated.
- A phase I study [Study 026, see Section 6.2.1.4] demonstrated the safety and tolerability of letermovir 480 mg administered by intravenous infusion over 60 minutes for 7 days.
- In order to avoid confusion at study sites, the infusion time and the volume of the final solution for infusion should be the same, regardless of the dose of letermovir (240 and 480 mg).

PMDA confirmed the rationale for the dosing regimen selected for the global phase III study (Study 001). The efficacy, safety, and dosage and administration of letermovir, etc. are discussed in Section 7.R.

6.R.3 Pharmacokinetic interactions

6.R.3.1 Drug interaction with voriconazole

The $AUC_{0\text{-}12}$ and C_{max} of voriconazole, which is a substrate of CYP2C9 and CYP2C19, were reduced by approximately 44% and 39%, respectively, when coadministered with letermovir [see Section 6.2.3]. The

intended population for letermovir is allo-HSCT recipients. These patients are at risk of fungal infection etc. and expected to use concomitant antifungals including voriconazole. PMDA asked the applicant to explain the effect of letermovir on the efficacy of voriconazole.

The applicant's explanation:
In a foreign phase II study (Study 020) and a global phase III study (Study 001) in allo-HSCT recipients, the occurrence of fungal infection-related events[59)] in patients who received concomitant voriconazole was assessed.

In the phase II study (Study 020), 60 of 131 subjects (16 of 33 subjects in the letermovir 60 mg group, 12 of 31 subjects in the letermovir 120 mg group, 19 of 34 subjects in the letermovir 240 mg group, 13 of 33 subjects in the placebo group) received concomitant voriconazole. In this patient subgroup, adverse events occurred in 2 of 16 subjects in the letermovir 60 mg group, 2 of 12 subjects in the letermovir 120 mg group, 1 of 19 subjects in the letermovir 240 mg group, and 0 of 13 subjects in the placebo group. None of these subjects experienced the event while receiving letermovir with voriconazole.

In the global phase III study (Study 001), 160 of 565 subjects (106 of 373 subjects in the letermovir group, 54 of 192 subjects in the placebo group) received concomitant voriconazole. In this patient subgroup, the incidences of opportunistic fungal infections during the study treatment period were 11.3% (12 of 106 subjects) in the letermovir group and 5.6% (3 of 54 subjects) in the placebo group. Among these subjects, 10 subjects experienced the event while receiving study drug with voriconazole (8 in the letermovir group, 2 in the placebo group), and the details of these cases were examined. As a result, it is difficult to conclude that the decreased voriconazole exposure when coadministered with letermovir affects the efficacy of voriconazole, but its possibility cannot be ruled out.

Taking account of the above results and the extent of decrease in voriconazole exposure, voriconazole will be listed in the precautions for concomitant use section of the package insert.

PMDA's view:
Although the information on concomitant use of letermovir with voriconazole in clinical studies is limited, the applicant's action (voriconazole will be listed in the precautions for concomitant use section of the package insert) is appropriate. This is based on the following findings: Voriconazole exposure was reduced when coadministered with letermovir [see Section 6.2.3], and the incidence of fungal infections was higher in the letermovir group than in the placebo group among patients who received concomitant voriconazole in the global phase III study (Study 001).

6.R.3.2 CYP2C8-mediated drug interactions

The applicant's explanation about CYP2C8-mediated drug interactions of letermovir:

[59)] Subjects who received at least 1 dose of voriconazole during the study treatment period were included in the analysis. Among adverse events in the MedDRA/J ver.13 SOC "Infections and infestations" for Study 020 or in the MedDRA/J ver.19 SOC "Infections and infestations" for Study 001, events coded to preferred terms (PTs) classified as fungal infection were identified.

The results of *in vitro* studies etc. suggested the potential for letermovir to cause drug interactions via CYP2C8 inhibition in clinical use [see Section 4.5.1]. Although no pharmacokinetic or safety clinical study with letermovir and a substrate of CYP2C8 has been conducted, simulations based on a Simcyp PBPK model[60] were performed to predict drug interactions between letermovir and substrates of CYP2C8 (repaglinide and rosiglitazone). The results are shown in Table 28. Letermovir may increase the plasma concentrations of these drugs via CYP2C8 inhibition. When letermovir is coadministered with these drugs, monitoring for the safety of the coadministered drug is recommended. Thus, CYP2C8 substrates such as repaglinide will be listed in the precautions for concomitant use section of the package insert.

Table 28. Results of simulations of drug interactions with PBPK model

Co-administered drug	Letermovir regimen	Geometric mean ratio (coadministration/administration alone) [90% CI]	
		AUC_{inf}	C_{max}
Repaglinide 1 mg single oral dose	480 mg PO QD for 10 days	2.34 [2.21, 2.48]	1.57 [1.52, 1.61]
	480 mg IV QD for 10 days	3.64 [3.41, 3.89]	1.78 [1.73, 1.83]
Rosiglitazone 4 mg single oral dose	480 mg PO QD for 10 days	1.40 [1.36, 1.45]	1.04 [1.03, 1.04]
	480 mg IV QD for 10 days	1.55 [1.49, 1.60]	1.05 [1.04, 1.06]

In a global phase III study (Study 001), 1 subject in the letermovir group and 2 subjects in the placebo group received a substrate of CYP2C8, repaglinide, during the study treatment period, and no adverse events related to diabetes mellitus or blood glucose control such as hypoglycemia were reported in the letermovir group.

PMDA's view:
Since CYP2C8 inhibition by letermovir was not evaluated in a clinical study, and drug interactions between letermovir and substrates of CYP2C8 were evaluated using the PBPK model only, drug interaction between letermovir and repaglinide in clinical use has not adequately been evaluated. Thus, at present, there is insufficient information to determine the appropriateness of listing repaglinide in the precautions for concomitant use section of the package insert.

When letermovir *in vitro* studies, static pharmacokinetic model, PBPK model, etc. showed the potential for letermovir to cause drug interactions via CYP2C8 inhibition in clinical use, a clinical drug interaction study of letermovir and a substrate of CYP2C8 should have been planned/conducted. Since the information on drug interactions between letermovir and substrates of CYP2C8 is limited at present, it is necessary to collect post-marketing information on the safety of letermovir when coadministered with a substrate of CYP2C8, etc. and appropriately provide any new finding to healthcare professionals in clinical practice as soon as possible.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from clinical studies shown in Table 29, with the application.

[60] The PBPK model of letermovir is a full PBPK model with first-order absorption and permeability-limited liver distribution, developed using the data from *in vitro* and clinical studies. The model predictive performance in predicting plasma concentration-time profiles following administration of multiple doses of letermovir in healthy subjects and HSCT recipients was assessed by comparison of simulated PK to observed PK data from clinical studies (CTD 5.3.5.3.5).

Table 29. Summary of clinical studies

Study Number (Phase)	Study population	No. of subjects evaluated	Regimen	Main endpoints
020 (Foreign phase II)	CMV-seropositive allo-HSCT recipients	133	Letermovir 60, 120, or 240 mg QD PO or placebo QD PO for 12 weeks	Efficacy Safety PK
001 (Global phase III)	CMV-seropositive allo-HSCT recipients	570	Letermovir 480 mg QD or 240 mg QD with cyclosporine, or placebo QD, PO or IV, through Week 14 post-transplant	Efficacy Safety

7.1 Foreign phase II study (CTD 5.3.5.1.2, Study 020 [March 2010 to October 2011])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 19 sites in Germany and the US to evaluate the efficacy, safety, and PK of letermovir in adult CMV-seropositive, allo-HSCT recipients (target sample size, 132 subjects). The key inclusion criteria for this study are shown below.

- Seropositive for CMV IgG antibodies within 1 year before transplantation.
- First allo-HSCT performed within 40 days before randomization for the treatment of leukaemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, or myelodysplastic or myeloproliferative disorder.
- Allogeneic human leukocyte antigen (HLA) (A, B, C, DR)-identical related or unrelated donor bone marrow or peripheral blood progenitor cell transplant recipient.
- Evidence of post-transplantation engraftment (absolute neutrophil count remaining ≥500/mm^3 for at least 3 consecutive sampling days).
- An active CMV replication not detectable within 5 days before starting study drug.

Letermovir 60, 120, or 240 mg or placebo QD was to be administered orally for 12 weeks (84 days).

Of 133 randomized subjects, 131 subjects who received at least 1 dose of study drug (33 in the letermovir 60 mg group, 31 in the letermovir 120 mg group, 34 in the letermovir 240 mg group, and 33 in the placebo group) were included in the safety population and in the full analysis set (FAS), and the FAS was used for efficacy analyses.

The primary efficacy endpoint of the incidence of CMV prophylaxis failure within the 84-day treatment period (defined as subjects who discontinued study drug because of the development of CMV viremia[61] or CMV end-organ disease, or for any other reason [e.g., an adverse event, withdrawal of consent]) was 48.5% (16 of 33 subjects) in the letermovir 60 mg group, 32.3% (10 of 31 subjects) in the letermovir 120 mg group, 29.4% (10 of 34 subjects) in the letermovir 240 mg group, and 63.6% (21 of 33 subjects) in the placebo group.

The incidences of adverse events (including abnormal laboratory changes) occurring on or after the initiation of study drug and within 7 days after the last dose of study drug were 93.9% (31 of 33 subjects) in the letermovir 60 mg group, 93.5% (29 of 31 subjects) in the letermovir 120 mg group, 100% (34 of 34 subjects)

[61] Systemic detectable CMV replication (2 blood samples positive for CMV antigen or DNA at 2 consecutive time points at a local laboratory, and at least 1 confirmed by PCR at the central laboratory), leading to discontinuation of study drug and initiation of treatment with an alternative CMV anti-viral medication.

in the letermovir 240 mg group, and 100% (33 of 33 subjects) in the placebo group, and the incidences of adverse drug reactions[62)] (including abnormal laboratory changes) were 33.3% (11 of 33 subjects) in the letermovir 60 mg group, 12.9% (4 of 31 subjects) in the letermovir 120 mg group, 5.9% (2 of 34 subjects) in the letermovir 240 mg group, and 33.3% (11 of 33 subjects) in the placebo group. Adverse events or adverse drug reactions reported in ≥10% of subjects in any group are shown in Table 30.

Table 30. Adverse events or adverse drug reactions reported in ≥10% of subjects in any group[a)] (Safety population)

Event term	Adverse events				Adverse drug reactions			
	60 mg (N = 33)	120 mg (N = 31)	240 mg (N = 34)	Placebo (N = 33)	60 mg (N = 33)	120 mg (N = 31)	240 mg (N = 34)	Placebo (N = 33)
Any event	31 (93.9)	29 (93.5)	34 (100)	33 (100)	11 (33.3)	4 (12.9)	2 (5.9)	11 (33.3)
Diarrhoea	9 (27.3)	9 (29.0)	11 (32.4)	10 (30.3)	4 (12.1)	0	1 (2.9)	2 (6.1)
Nausea	7 (21.2)	8 (25.8)	7 (20.6)	11 (33.3)	1 (3.0)	0	0	2 (6.1)
Vomiting	4 (12.1)	10 (32.3)	8 (23.5)	4 (12.1)	3 (9.1)	1 (3.2)	1 (2.9)	0
Constipation	4 (12.1)	3 (9.7)	3 (8.8)	1 (3.0)	0	0	0	0
Abdominal pain	3 (9.1)	3 (9.7)	3 (8.8)	5 (15.2)	1 (3.0)	0	0	1 (3.0)
Dyspepsia	1 (3.0)	2 (6.5)	4 (11.8)	1 (3.0)	0	1 (3.2)	1 (2.9)	1 (3.0)
Abdominal pain upper	1 (3.0)	2 (6.5)	4 (11.8)	2 (6.1)	0	1 (3.2)	0	0
Dry mouth	1 (3.0)	1 (3.2)	1 (2.9)	4 (12.1)	0	0	0	1 (3.0)
CMV infection	6 (18.2)	6 (19.4)	5 (14.7)	11 (33.3)	0	0	0	0
Candidiasis	4 (12.1)	1 (3.2)	1 (2.9)	3 (9.1)	0	0	0	0
Nasopharyngitis	0	0	4 (11.8)	0	0	0	0	0
Rash	4 (12.1)	5 (16.1)	4 (11.8)	6 (18.2)	1 (3.0)	1 (3.2)	0	0
Pruritus	2 (6.1)	4 (12.9)	5 (14.7)	3 (9.1)	0	0	0	0
Erythema	0	4 (12.9)	4 (11.8)	2 (6.1)	0	0	0	0
Fatigue	3 (9.1)	8 (25.8)	4 (11.8)	5 (15.2)	1 (3.0)	0	0	1 (3.0)
Oedema peripheral	4 (12.1)	3 (9.7)	8 (23.5)	3 (9.1)	2 (6.1)	0	0	0
Pyrexia	3 (9.1)	4 (12.9)	5 (14.7)	6 (18.2)	0	0	0	1 (3.0)
Decreased appetite	4 (12.1)	2 (6.5)	5 (14.7)	3 (9.1)	1 (3.0)	0	0	0
Hyperkalaemia	4 (12.1)	2 (6.5)	2 (5.9)	1 (3.0)	0	0	0	0
Cough	2 (6.1)	8 (25.8)	5 (14.7)	1 (3.0)	0	0	0	0
Headache	4 (12.1)	3 (9.7)	8 (23.5)	3 (9.1)	1 (3.0)	1 (3.2)	0	1 (3.0)
Back pain	2 (6.1)	4 (12.9)	2 (5.9)	1 (3.0)	0	0	0	0
Muscle spasms	1 (3.0)	2 (6.5)	4 (11.8)	0	1 (3.0)	0	0	0
Acute graft versus host disease in skin	3 (9.1)	5 (16.1)	6 (17.6)	2 (6.1)	0	0	0	0
Acute graft versus host disease in intestine	3 (9.1)	0	5 (14.7)	4 (12.1)	0	0	0	0
Renal failure	5 (15.2)	5 (16.1)	3 (8.8)	2 (6.1)	1 (3.0)	0	0	1 (3.0)
Dry eye	1 (3.0)	2 (6.5)	5 (14.7)	1 (3.0)	0	0	0	0
Anaemia	3 (9.1)	2 (6.5)	4 (11.8)	2 (6.1)	0	0	0	0
Insomnia	5 (15.2)	4 (12.9)	2 (5.9)	0	1 (3.0)	0	0	0

n (%)
a) Occurring on or after initiation of study drug and within 7 days after the last dose of study drug

Between the time of initiation of study drug and 7 days following the last dose of study drug, there were 2 deaths in the letermovir 60 mg group (acute graft versus host disease in intestine; and acute myeloid leukaemia, 1 subject each), 1 death in the letermovir 240 mg group (pneumonia), and 1 death in the placebo group (pneumonia bacterial), and a causal relationship to study drug was denied for all those cases. After the end of the follow-up period, 1 death occurred in the letermovir 120 mg group (pneumonia), but its causal relationship to study drug was denied.

Between the time of initiation of study drug and 7 days following the last dose of study drug, serious adverse events occurred in 9 subjects in the letermovir 60 mg group (acute graft versus host disease in intestine [2 subjects]; pneumonia; Epstein-Barr virus infection; alcaligenes infection; acute myeloid leukaemia; leukaemia

62) Adverse events assessed by the investigator as possibly, probably, or definitely related to study drug.

recurrent; diabetic ketoacidosis; hyperkalaemia; hypoglycaemia; liver function test; pyrexia; and spinal compression fracture, 1 subject each [some subjects were counted more than once because more than one event occurred]), 12 subjects in the letermovir 120 mg group (pneumonia; CMV infection; enterococcal bacteraemia; pneumonia respiratory syncytial viral; septic shock; acute myeloid leukaemia; acute lymphocytic leukaemia; diffuse large B-cell lymphoma recurrent; myelodysplastic syndrome; loss of consciousness; paraesthesia; syncope; gastritis; vomiting; hepatic enzyme increased; febrile neutropenia; venoocclusive liver disease; and pulmonary embolism, 1 subject each [some subjects were counted more than once because more than one event occurred]), 9 subjects in the letermovir 240 mg group (pneumonia; and acute graft versus host disease in intestine [2 subjects each]; Epstein-Barr virus infection; bacteraemia; clostridial infection; human herpesvirus 6 infection; oral infection; pneumonia primary atypical; leukaemia recurrent; lymphoma; and pericarditis, 1 subject each [some subjects were counted more than once because more than one event occurred]), and 12 subjects in the placebo group (CMV infection; and pyrexia [2 subjects each]; pneumonia primary atypical; device related infection; enterobacter infection; herpes virus infection; pneumonia bacterial; upper respiratory tract infection; acute myeloid leukaemia [in remission]; acute graft versus host disease in intestine; acute graft versus host disease in skin; convulsion; nausea; and febrile neutropenia, 1 subject each [some subjects were counted more than once because more than one event occurred]). A causal relationship to study drug was denied for all those events.

Adverse events leading to study drug discontinuation occurred in 9 subjects in the letermovir 60 mg group (CMV infection [5 subjects]; liver function test; ALT increased; AST increased; blood ALP increased; CMV test positive; acute graft versus host disease in intestine; acute graft versus host disease in liver; vomiting; diarrhoea; and cholelithiasis, 1 subject each [some subjects were counted more than once because more than one event occurred]), 9 subjects in the letermovir 120 mg group (CMV infection [6 subjects]; hepatic enzyme increased; transaminases increased; venoocclusive liver disease; and neutropenia, 1 subject each [some subjects were counted more than once because more than one event occurred]), 7 subjects in the letermovir 240 mg group (CMV infection [2 subjects]; human herpesvirus 6 infection; gamma-glutamyltransferase increased; acute graft versus host disease in intestine; vomiting; and lymphoma, 1 subject each), and 19 subjects in the placebo group (CMV infection [10 subjects]; nausea; neutropenia; pyrexia; and headache [2 subjects each]; CMV viremia, device related infection; pneumonia bacterial; CMV test positive; diarrhoea; abdominal pain; vision blurred; and chills, 1 subject each [some subjects were counted more than once because more than one event occurred]), among which, the events reported by 2 subjects in the letermovir 60 mg group (ALT increased; AST increased; blood ALP increased; vomiting; and diarrhoea, 1 subject each [some subjects were counted more than once because more than one event occurred]), 1 subject in the letermovir 120 mg group (transaminases increased), 2 subjects in the letermovir 240 mg group (vomiting; and gamma-glutamyltransferase increased, 1 subject each), and 3 subjects in the placebo group (headache; pyrexia; nausea; abdominal pain; diarrhoea; and vision blurred, 1 subject each [some subjects were counted more than once because more than one event occurred]) were assessed as causally related to study drug. The outcomes of the events reported by 1 subject in the letermovir 120 mg group (transaminases increased) and 1 subject in the letermovir 240 mg group (gamma-glutamyltransferase increased) were reported as "unresolved" and other events resolved.

7.2 Global phase III study (CTD 5.3.5.1.3, Study 001 [June 2014 to September 2016])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 67 sites in 20 countries including Japan, the US, and Spain to evaluate the efficacy and safety of letermovir in adult allo-HSCT recipients who were seropositive for CMV IgG antibodies (target sample size, 540 subjects). The key inclusion criteria for this study are shown below.

- Seropositivity for CMV within 1 year before transplantation.
- Received a first allo-HSCT (bone marrow, peripheral blood stem cell, or cord blood transplant) and been within 28 days post-HSCT at the time of randomization.
- Undetectable CMV DNA from a plasma sample collected within 5 days prior to randomization.

Based on the results of exposure-response analyses using the data from a foreign phase II study (Study 020), etc., letermovir 480 mg (240 mg with concomitant cyclosporine) or placebo QD was to be administered orally or by intravenous infusion over 60 minutes[63] [see Section 6.R.2]. Study drug was to be initiated any time from the day of transplantation until 28 days post-transplantation, and each subject was to receive study drug through Week 14 post-transplant.

Of 570 randomized subjects, 565 subjects who received at least 1 dose of study drug (373 in the letermovir group, 192 in the placebo group) were included in the safety population. After excluding 48 subjects in the letermovir group and 22 subjects in the placebo group who had detectable CMV DNA on Day 1, 495 subjects (325 in the letermovir group, 170 in the placebo group) were included in the FAS (efficacy population). The safety population and the efficacy population included 35 Japanese subjects (24 in the letermovir group, 11 in the placebo group) and 30 Japanese subjects (24 in the letermovir group, 6 in the placebo group), respectively.

The primary efficacy endpoint of the proportion of subjects with clinically significant CMV infection (defined as the onset of CMV end-organ disease, or the initiation of anti-CMV preemptive therapy[64] based on documented CMV viremia and the clinical condition of the subject) through Week 24 post-transplant[65] was 37.5% (122 of 325 subjects) in the letermovir group and 60.6% (103 of 170 subjects) in the placebo group. The treatment difference [95.02% CI] was −23.5 [−32.6, −14.5]%, demonstrating the superiority of letermovir over placebo [the one-sided P-value <0.0001, a one-sided significance level of 0.0249, the Mantel-

63) As a rule, patients were to be initiated with the oral (tablet) formulation of study therapy. For patients who could not swallow tablets and/or had a condition (e.g., vomiting, diarrhea, or malabsorption) that may interfere with the absorption of the study drug, the use of the IV formulation was allowed. The IV formulation was to be switched to oral study therapy as soon as such patients were able to swallow and/or the condition necessitating the use of the IV formulation resolved. Use of the IV formulation was generally limited to 4 weeks or less in duration. However, it was left to the investigator's discretion to continue IV administration beyond 4 weeks, according to the subject's condition.

64) Defined as CMV viremia confirmed by measuring the plasma level of CMV DNA at the central laboratory and initiation of preemptive therapy with GCV, valganciclovir, foscarnet, or cidofovir (unapproved in Japan). The protocol specified the viral load thresholds for preemptive therapy initiation as follows (CMV DNA ≥150 copies/mL for high-risk patients and CMV DNA >300 copies/mL for low-risk patients during the study treatment period [through Week 14 post-transplant]; CMV DNA >300 copies/mL for all patients thereafter).

65) Patients who discontinued the study before Week 24 post-transplant or had missing efficacy data at Week 24 post-transplant were considered as failures for analyses.

Haenszel method, with stratification according to CMV infection risk group (high risk/low risk)[66)]].

In the Japanese subgroup, the proportions of patients with clinically significant CMV infection through Week 24 post-transplant were 54.2% (13 of 24 subjects) in the letermovir group and 50.0% (3 of 6 subjects) in the placebo group.

The incidences of adverse events (including abnormal laboratory changes) occurring during the treatment phase (through 14 days after the last dose of study drug) were 97.9% (365 of 373 subjects) in the letermovir group and 100% (192 of 192 subjects) in the placebo group, and the incidences of adverse drug reactions (including abnormal laboratory changes) were 16.9% (63 of 373 subjects) in the letermovir group and 12.0% (23 of 192 subjects) in the placebo group. Adverse events or adverse drug reactions reported in ≥5% of subjects in either group are shown in Table 31.

Table 31. Adverse events or adverse drug reactions reported in ≥5% of subjects in either group (Treatment phase, Safety population)

Event term	Adverse events		Adverse drug reactions	
	Letermovir (N = 373)	Placebo (N = 192)	Letermovir (N = 373)	Placebo (N = 192)
Any event	365 (97.9)	192 (100)	63 (16.9)	23 (12.0)
Anaemia	25 (6.7)	10 (5.2)	1 (0.3)	0
Febrile neutropenia	31 (8.3)	18 (9.4)	0	0
Thrombocytopenia	25 (6.7)	11 (5.7)	1 (0.3)	0
Dry eye	22 (5.9)	10 (5.2)	1 (0.3)	0
Abdominal pain	44 (11.8)	18 (9.4)	3 (0.8)	1 (0.5)
Abdominal pain upper	15 (4.0)	16 (8.3)	0	0
Constipation	27 (7.2)	20 (10.4)	0	2 (1.0)
Diarrhoea	97 (26.0)	47 (24.5)	9 (2.4)	2 (1.0)
Dry mouth	20 (5.4)	6 (3.1)	0	0
Dyspepsia	20 (5.4)	7 (3.6)	1 (0.3)	0
Nausea	99 (26.5)	45 (23.4)	27 (7.2)	7 (3.6)
Stomatitis	23 (6.2)	9 (4.7)	0	1 (0.5)
Vomiting	69 (18.5)	26 (13.5)	7 (1.9)	2 (1.0)
Asthenia	23 (6.2)	7 (3.6)	0	0
Fatigue	50 (13.4)	21 (10.9)	2 (0.5)	1 (0.5)
Mucosal inflammation	46 (12.3)	24 (12.5)	0	0
Oedema peripheral	54 (14.5)	18 (9.4)	2 (0.5)	1 (0.5)
Pyrexia	77 (20.6)	43 (22.4)	0	1 (0.5)
Graft versus host disease	146 (39.1)	74 (38.5)	0	0
Bacteraemia	20 (5.4)	4 (2.1)	0	0
CMV infection	31 (8.3)	88 (45.8)	0	0
Pneumonia	20 (5.4)	5 (2.6)	0	0
Viraemia	11 (2.9)	11 (5.7)	0	0
ALT increased	24 (6.4)	16 (8.3)	3 (0.8)	2 (1.0)
AST increased	19 (5.1)	13 (6.8)	2 (0.5)	2 (1.0)
Blood creatinine increased	36 (9.7)	13 (6.8)	3 (0.8)	1 (0.5)
Decreased appetite	38 (10.2)	22 (11.5)	2 (0.5)	0
Hyperglycaemia	25 (6.7)	10 (5.2)	0	0
Hyperkalaemia	27 (7.2)	4 (2.1)	0	0
Hypokalaemia	22 (5.9)	11 (5.7)	0	1 (0.5)
Hypomagnesaemia	23 (6.2)	15 (7.8)	0	0
Hyponatraemia	21 (5.6)	10 (5.2)	0	0
Arthralgia	26 (7.0)	10 (5.2)	0	0
Back pain	23 (6.2)	14 (7.3)	0	1 (0.5)
Myalgia	19 (5.1)	3 (1.6)	0	0

66) Risk for CMV infection was defined as follows:
High risk: Patients meeting one or more of the following criteria at the time of randomization: (1) HLA-related (sibling) donor with at least one mismatch at one of the following 3 HLA-gene loci: HLA-A, -B, or -DR, (2) Haploidentical donor, (3) Unrelated donor with at least one mismatch at one of the following 4 HLA-gene loci: HLA-A, -B, -C or -DRB1, (4) Use of umbilical cord blood as stem cell source, (5) Use of *ex vivo* T-cell-depleted grafts (including *ex vivo* use of alemtuzumab [unapproved in Japan]), (6) Grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as corticosteroids equivalent to ≥1 mg/kg/day prednisolone).
Low risk: All patients not meeting the definition of high risk.

Event term	Adverse events		Adverse drug reactions	
	Letermovir (N = 373)	Placebo (N = 192)	Letermovir (N = 373)	Placebo (N = 192)
Any event	365 (97.9)	192 (100)	63 (16.9)	23 (12.0)
Pain in extremity	19 (5.1)	11 (5.7)	0	0
Dizziness	25 (6.7)	11 (5.7)	0	0
Headache	52 (13.9)	18 (9.4)	2 (0.5)	0
Tremor	27 (7.2)	8 (4.2)	0	0
Anxiety	20 (5.4)	5 (2.6)	0	0
Insomnia	34 (9.1)	10 (5.2)	0	0
Acute kidney injury	36 (9.7)	25 (13.0)	1 (0.3)	1 (0.5)
Cough	53 (14.2)	20 (10.4)	0	0
Dyspnoea	30 (8.0)	6 (3.1)	1 (0.3)	0
Epistaxis	23 (6.2)	11 (5.7)	0	1 (0.5)
Oropharyngeal pain	28 (7.5)	15 (7.8)	0	0
Dry skin	26 (7.0)	8 (4.2)	0	0
Erythema	33 (8.8)	11 (5.7)	1 (0.3)	0
Pruritus	26 (7.0)	11 (5.7)	1 (0.3)	0
Rash	76 (20.4)	41 (21.4)	1 (0.3)	2 (1.0)
Hypertension	31 (8.3)	21 (10.9)	0	1 (0.5)

n (%)

Adverse events leading to death occurred in 38 subjects in the letermovir group and 17 subjects in the placebo group, as listed in Table 32. A causal relationship to study drug was denied for all those events. During the follow-up period between 14 days after the last dose of study drug and Week 24 after transplantation, adverse events leading to death occurred in 23 subjects in the letermovir group and 21 subjects in the placebo group, but a causal relationship to study drug was denied for all those events.

Table 32. Adverse events leading to death (Treatment phase)

Letermovir (N = 373)	38 subjects (acute myeloid leukaemia recurrent [7 subjects]; graft versus host disease [5 subjects]; sepsis; and septic shock [3 subjects each]; pneumonia; acute lymphocytic leukaemia recurrent; acute myeloid leukaemia; and respiratory failure [2 subjects each]; thrombocytopenia; cardiac failure; acute hepatic failure; venoocclusive liver disease; bronchopulmonary aspergillosis; Klebsiella sepsis; acute lymphocytic leukaemia; diffuse large B-cell lymphoma recurrent; mantle cell lymphoma; mycosis fungoides; mycosis fungoides recurrent; natural killer-cell leukaemia; plasma cell myeloma recurrent; and venoocclusive disease, 1 subject each)
Placebo (N = 192)	17 subjects (graft versus host disease; septic shock; and acute myeloid leukaemia recurrent [3 subjects each]; venoocclusive liver disease [2 subjects]; immune thrombocytopenic purpura; cardiogenic shock; multiple organ dysfunction syndrome; hepatic function abnormal; bacterial sepsis; bronchopulmonary aspergillosis; pneumocystis jirovecii pneumonia; sepsis; acute myeloid leukaemia; and myelodysplastic syndrome, 1 subject each)

Serious adverse events occurred in 165 subjects in the letermovir group and 90 subjects in the placebo group, and the main events are shown in Table 33. The events reported by 3 subjects in the letermovir group (pancytopenia; thrombocytopenia; and delayed engraftment, 1 subject each) and 3 subjects in the placebo group (Bowen's disease; mental status changes; and acute kidney injury, 1 subject each) were assessed as causally related to study drug, and the outcome of the event reported by 1 subject in the letermovir group (pancytopenia) was reported as "unchanged" and the outcomes of other events were reported as "recovered/resolved." During the follow-up period between 14 days after the last dose of study drug and Week 24 after transplantation, serious adverse events occurred in 28 subjects in the letermovir group and 19 subjects in the placebo group, but a causal relationship to study drug was denied for all those events.

Table 33. Serious adverse events (Treatment phase)

Letermovir (N = 373)	165 subjects (graft versus host disease [37 subjects]; acute myeloid leukaemia recurrent [11 subjects]; CMV infection [10 subjects]; pneumonia [8 subjects]; pyrexia [7 subjects]; acute kidney injury [5 subjects]; septic shock [4 subjects]; diarrhoea [2 subjects], etc.)
Placebo (N = 192)	90 subjects (graft versus host disease [20 subjects]; CMV infection [13 subjects]; acute kidney injury [9 subjects]; septic shock [5 subjects]; acute myeloid leukaemia recurrent [7 subjects]; diarrhoea [5 subjects]; pyrexia [4 subjects]; pneumonia [3 subjects], etc.)

Adverse events leading to study drug discontinuation occurred in 72 subjects in the letermovir group and 98 subjects in the placebo group, as listed in Table 34. The events reported by 18 subjects in the letermovir group (nausea [6 subjects]; vomiting [3 subjects]; abdominal pain [2 subjects]; anaemia; pancytopenia; thrombocytopenia; diarrhoea; hypersensitivity; delayed engraftment; blood creatinine increased; and confusional state [1 subject each] [some subjects were counted more than once because more than one event occurred]) and 7 subjects in the placebo group (nausea [2 subjects]; mouth ulceration; blood creatinine increased; Bowen's disease; mental status changes; and acute kidney injury [1 subject each]) were assessed as causally related to study drug, and the outcomes of the events reported by 1 subject in the letermovir group (pancytopenia) and 1 subject in the placebo group (blood creatinine increased) were reported as "not recovered" and the outcomes of other events were reported as "recovered or recovering/resolving."

Table 34. Adverse events leading to study drug discontinuation

Letermovir (N = 373)	72 subjects (CMV infection [23 subjects]; nausea [6 subjects]; acute myeloid leukaemia recurrent [4 subjects]; vomiting; and graft versus host disease [3 subjects each]; thrombocytopenia; abdominal pain; venoocclusive liver disease; pneumonia; and blood creatinine increased [2 subjects each]; anaemia; leukopenia; neutropenia; pancytopenia; cardiac failure; diarrhoea; acute hepatic failure; hypersensitivity; bronchopulmonary aspergillosis; herpes zoster; meningoencephalitis herpetic; sepsis; septic shock; viraemia; delayed engraftment; hepatic enzyme increased; myelodysplastic syndrome; cerebral haemorrhage; encephalopathy; headache; confusional state; respiratory failure; rash; and venoocclusive disease [1 subject each])
Placebo (N = 192)	98 subjects (CMV infection [75 subjects]; nausea; venoocclusive liver disease; graft versus host disease; and septic shock [2 subjects each]; neutropenia; diarrhoea; mouth ulceration; bacterial sepsis; bronchopulmonary aspergillosis; oral herpes; pneumocystis jirovecii pneumonia; subdural haematoma; ALT increased; blood creatinine increased; acute myeloid leukaemia recurrent; Bowen's disease; myelodysplastic syndrome; mental status changes; and acute kidney injury [1 subject each])

In the Japanese subgroup, the incidences of adverse events (including abnormal laboratory changes) occurring during the treatment phase were 100% (24 of 24 subjects) in the letermovir group and 100% (11 of 11 subjects) in the placebo group, and the incidences of adverse drug reactions (including abnormal laboratory changes) were 16.7% (4 of 24 subjects) in the letermovir group and 18.2% (2 of 11 subjects) in the placebo group. Adverse events reported in ≥2 subjects in either group are shown in Table 35.

Table 35. Adverse events or adverse drug reactions reported in ≥2 subjects in either group (Treatment phase, Japanese subgroup)

Event term	Adverse events		Adverse drug reactions	
	Letermovir (N = 24)	Placebo (N = 11)	Letermovir (N = 24)	Placebo (N = 11)
Any event	24 (100)	11 (100)	4 (16.7)	2 (18.2)
Palpitations	2 (8.3)	0	0	0
Conjunctival haemorrhage	2 (8.3)	0	0	0
Abdominal pain	3 (12.5)	0	0	0
Nausea	2 (8.3)	0	1 (4.2)	0
Vomiting	2 (8.3)	1 (9.1)	1 (4.2)	0
Pyrexia	3 (12.5)	2 (18.2)	0	0
Hepatic function abnormal	4 (16.7)	2 (18.2)	0	1 (9.1)
Graft versus host disease	9 (37.5)	6 (54.5)	0	0
Bacteraemia	2 (8.3)	0	0	0
CMV infection	2 (8.3)	7 (63.6)	0	0
Nasopharyngitis	2 (8.3)	0	0	0
Pneumonia	3 (12.5)	0	0	0
Sepsis	3 (12.5)	1 (9.1)	0	0

Event term	Adverse events		Adverse drug reactions	
	Letermovir (N = 24)	Placebo (N = 11)	Letermovir (N = 24)	Placebo (N = 11)
Any event	24 (100)	11 (100)	4 (16.7)	2 (18.2)
AST increased	2 (8.3)	0	0	0
Staphylococcus test positive	2 (8.3)	0	0	0
Decreased appetite	3 (12.5)	0	1 (4.2)	0
Hyperglycaemia	2 (8.3)	1 (9.1)	0	0
Hypokalaemia	2 (8.3)	1 (9.1)	0	0
Arthralgia	2 (8.3)	0	0	0
Musculoskeletal stiffness	0	2 (18.2)	0	0
Headache	3 (12.5)	1 (9.1)	0	0
Hypoaesthesia	2 (8.3)	0	0	0
Renal impairment	3 (12.5)	2 (18.2)	1 (4.2)	1 (9.1)
Rash	8 (33.3)	2 (18.2)	0	1 (9.1)
Hypertension	2 (8.3)	0	0	0

n (%)

An adverse event leading to death occurred in 1 subject in the letermovir group (cardiac failure), and its causal relationship to study drug was denied.

Serious adverse events occurred in 3 subjects in the letermovir group (cardiac failure; bronchopulmonary aspergillosis; and platelet count decreased, 1 subject each) and 1 subject in the placebo group (adenoviral haemorrhagic cystitis), and a causal relationship to study drug was denied for all those events. During the follow-up period between 14 days after the last dose of study drug and Week 24 after transplantation, an adverse event leading to death occurred in 1 subject in the placebo group (acute myeloid leukaemia recurrent) and a non-fatal serious adverse event occurred in 1 subject in the placebo group (decreased appetite), but a causal relationship to study drug was denied for both events.

Adverse events leading to study drug discontinuation occurred in 5 subjects in the letermovir group (CMV infection [2 subjects]; vomiting; cardiac failure; and bronchopulmonary aspergillosis, 1 subject each) and 5 subjects in the placebo group (CMV infection [5 subjects]). The event reported by 1 subject in the letermovir group (vomiting) was assessed as causally related to study drug, but resolved following treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package

For this application, a clinical data package was constructed based on the results from clinical studies including a global phase III study (Study 001) in CMV-seropositive allo-HSCT recipients.

The applicant's explanation about the appropriateness of evaluating the efficacy and safety of letermovir in Japanese patients based on the results from clinical studies including a global phase III study (Study 001):
Since CMV disease may become severe, leading to a serious outcome, the Japanese and foreign clinical practice guidelines recommend preventive measures against CMV disease after allo-HSCT (Guideline of Japan Society for Hematopoietic Cell Transplantation, Volume 1, *Medicine and Drug Journal*. 2014;126-61, *Biol Blood Marrow Transplant.* 2009;15:1143-238). Preventive measures against CMV disease for allo-HSCT recipients, etc. in Japan and overseas are shown in Table 36.

Table 36. Preventive measures against CMV disease for allo-HSCT recipients, etc. in Japan and overseas

		Japan	Overseas
Clinical practice guidelines [Japan, Guideline of Japan Society for Hematopoietic Cell Transplantation, Volume 1, *Medicine and Drug Journal.* 2014;126-61; Overseas, *Biol Blood Marrow Transplant.* 2009;15:1143-238]	Preventive measures against CMV disease	For the prevention of CMV disease in CMV-seropositive allo-HSCT recipients, prophylactic therapy (prophylactic administration of antivirals after hematopoietic recovery) and preemptive therapy (monitoring for CMV reactivation with initiation of antivirals if CMV viremia at levels above a threshold is detected) are available. At present, preemptive therapy is the mainstay. There are no drugs approved for prophylactic therapy in Japan. GCV is used as a first-line drug for preemptive therapy, and foscarnet is used as an alternative.	Allo-HSCT recipients at risk for post-transplant CMV disease should be placed on a CMV disease prevention program from the time of engraftment until at least 100 days after HSCT. Physicians should use either prophylaxis or preemptive treatment. In selecting a CMV disease prevention strategy, physicians should assess the risks and benefits of each strategy, the needs and condition of the patient, and the hospital's virology laboratory support capability. GCV is used as a first-line drug. In addition, foscarnet or cidofovir (unapproved in Japan) is used for preemptive therapy, and foscarnet, acyclovir, or valacyclovir is used for prophylactic therapy.
	Threshold for initiation of preemptive therapy	Monitoring for CMV reactivation with initiation of preemptive therapy in patients at high risk for CMV disease. The threshold for initiation of preemptive therapy or the dose levels have not been standardized, and a decision should be made, according to each patient's risk.	HSCT recipients who are ≤100 days after HSCT should begin preemptive treatment with GCV if CMV antigenemia or CMV DNA is detected by blood test.
Distribution of CMV gB genotypes		gB 1 and gB 3 were more prevalent, and gB 2 and gB 4 were less prevalent (*Arch Virol.* 2008;153:667-74, *J Med Virol.* 2015;87:1441-5, etc.).	gB 1 and gB 2 were more prevalent in Germany (*Antiviral Res.* 2016;132:204-9). Geographic (the US, Italy, Zimbabwe) and demographic differences in the frequency of gB genotypes have been reported (*AIDS Res Hum Retroviruses.* 1988;14:533-6).

"Preemptive therapy" is recommended as a preventive measure against CMV disease. According to the aforementioned Japanese clinical practice guideline, preemptive therapy is used for CMV disease prevention in allo-HSCT recipients: monitoring for CMV reactivation after HSCT with the initiation of antivirals in patients at high risk for CMV disease. However, the threshold for the initiation of preemptive therapy, etc. have not been standardized, and it is necessary to make a decision according to an individual patient's risk. Even if low-level CMV viremia is detected after HSCT, CMV viremia may become undetectable without treatment or viral replication may result in the development of CMV disease. Thus, physicians in clinical practice determine the need for preemptive treatment, according to an individual patient's risk factors or clinical condition. In Study 001, since the initiation of preemptive therapy is an important factor for efficacy evaluation of letermovir, the protocol provided a guidance on the blood CMV DNA thresholds for preemptive therapy initiation (≥150 copies/mL or >300 copies/mL according to CMV disease risk, etc.).[64)]

Although it was suggested that the distribution of CMV gB genotypes differs between Japan and overseas, the antiviral activity of letermovir against all gB genotypes was demonstrated [see Section 3.1.1.2].

According to the PK data from phase I studies, which were conducted prior to the initiation of Study 001, letermovir exposure was higher in Japanese healthy subjects than in non-Japanese healthy subjects, but the safety in Japanese subjects was favorable [see Section 6.R.1].

Based on the above, there are some differences in preventive measures against CMV disease for allo-HSCT recipients, the distribution of CMV gB genotypes, etc. between Japan and overseas, which were not considered to have a significant impact on the efficacy and safety of letermovir. Thus, the applicant selected a development

strategy in which Japan participates in the global phase III study (Study 001), from the standpoint of the feasibility of a Japanese clinical study in allo-HSCT recipients, etc.

Since Study 001 demonstrated the efficacy and safety of letermovir [see Section 7.R.2 and Section 7.R.3], the applicant concluded that the efficacy and safety of letermovir in Japanese patients can be evaluated, based on a clinical data package including the results from Study 001.

PMDA considers that the applicant's explanation is acceptable and evaluates the efficacy and safety of letermovir in Japanese patients, based on the results from clinical studies including the global phase III study (Study 001). The efficacy and safety of letermovir are discussed in Section 7.R.2 and Section 7.R.3.

7.R.2 Efficacy

Based on the following considerations, PMDA concluded that the efficacy of letermovir in the prophylaxis of CMV disease in Japanese allo-HSCT recipients is expected.

However, since there is limited clinical experience with letermovir in Japanese allo-HSCT recipients and the information on the efficacy of the IV formulation is limited, it is necessary to collect post-marketing information on the efficacy of letermovir in Japanese allo-HSCT recipients, including the information on the route of administration, and appropriately provide the obtained information to healthcare professionals in clinical practice. It is important to collect post-marketing information on letermovir resistance mutations, including the published literature, and provide any new finding to healthcare professionals in clinical practice.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.2.1 Efficacy in global phase III study (Study 001)

The applicant's explanation about the rationale for the primary efficacy endpoint for Study 001 in allo-HSCT recipients:

Letermovir was to be developed as a drug for use in CMV prophylactic strategy in allo-HSCT recipients, and the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant was chosen as the primary endpoint for Study 001. Clinically significant CMV infection was defined as the occurrence of either one of the following outcomes.

- Onset of CMV end-organ disease
- Initiation of anti-CMV preemptive therapy based on documented CMV viremia and the clinical condition of the subject[64)]

Since CMV disease may lead to a deteriorated general condition or a serious outcome in HSCT recipients, the Japanese and foreign clinical practice guidelines recommend preemptive therapy as a preventive measure against CMV disease [see Section 7.R.1]. Though no common thresholds exist for the initiation of preemptive therapy in Japan and overseas, preemptive therapy with GCV etc. is used according to an individual patient's clinical condition, before the onset of CMV disease, after the detection of CMV viremia, at many HCT centers

in Japan and overseas (*Biol Blood Marrow Transplant*. 2011;17:664-73). The introduction of preemptive therapy has been reported to have reduced the incidence of CMV disease during the first 100 days after transplantation, during which allo-HSCT recipients are at highest risk for developing CMV disease, compared to the incidence before the widespread use of preemptive therapy (*Hematology Am Soc Hematol Educ Program*. 2011;2011:305-9, *Blood.* 2004;103:2003-8, etc.), and preemptive therapy is considered important for the prevention of CMV disease. On the other hand, it has been reported that CMV reactivation is associated with an increased risk of overall mortality in the first year after transplantation, independent of the use of preemptive therapy, and with higher viral loads associated with higher risk of death (*Lancet Haematol.* 2016;3:e119-27), and the prevention of CMV viremia is also considered important for the prognosis of HSCT recipients. Thus, the definition of the primary endpoint of "clinically significant CMV infection" for Study 001 included both the onset of CMV disease and the initiation of preemptive therapy based on CMV viremia.

It has been reported that without a preventive measure against CMV disease after allo-HSCT, CMV reactivation usually occurs within the first 24 weeks after transplantation, and that the risk of CMV reactivation is highest particularly during the first 14 weeks (approximately 100 days) after transplantation (*Bone Marrow Transplant.* 2007;40:125-36, *Lancet Infect Dis.* 2011;11:284-92, etc.). Thus, the treatment duration was through Week 14 post-transplant, and the primary efficacy endpoint was evaluated at Week 24 post-transplant in Study 001.

The applicant's explanation about the efficacy of letermovir in the prophylaxis of CMV disease:
(a) Overall population
The primary endpoint of the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant [65] was 37.5% (122 of 325 subjects) in the letermovir group and 60.6% (103 of 170 subjects) in the placebo group, and the treatment difference [95.02% CI] was −23.5 [−32.6, −14.5]%.[67] A pairwise comparison showed a statistically significant difference, and the superiority of letermovir over placebo was demonstrated [see Section 7.2]. The results of subgroup analyses, i.e. the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant by risk stratum, conditioning regimen, and concomitant immunosuppressive regimen is shown in Table 37. The proportion of subjects with clinically significant CMV infection was lower in the letermovir group than in the placebo group across all subgroups.

[67] Calculated using the Mantel-Haenszel method, with stratification according to CMV infection risk group (high risk/low risk)

Table 37. Subgroup analyses of Study 001 (FAS)[a)]

		Letermovir	Placebo	Treatment difference [95% CI]
CMV infection risk stratum[b)]	High risk	42.2 (43/102)	73.3 (33/45)	-31.2 [-47.5, -14.9]
	Low risk	35.4 (79/223)	56.0 (70/125)	-20.6 [-31.3, -9.8]
Conditioning regimen	Myeloablative	39.0 (60/154)	58.8 (50/85)	-20.9 [-33.9, -7.9]
	Reduced-intensity	38.4 (33/86)	58.3 (28/48)	-19.9 [-37.7, -2.2]
	Nonmyeloablative	34.1 (29/85)	67.6 (25/37)	-33.2 [-51.4, -15.0]
Immunosuppressive regimen[c)]	Cyclosporine	35.8 (58/162)	66.7 (60/90)	-31.1 [-43.2, -19.0]
	Tacrolimus	38.6 (56/145)	53.6 (37/69)	-15.5 [-29.8, -1.1]
	Others	44.4 (8/18)	55.6 (5/9)	—
	Unknown	—	50.0 (1/2)	—

% (n/N) —: Not applicable

a) Patients who discontinued the study before Week 24 post-transplant or had missing efficacy data at Week 24 post-transplant were considered as failures.

b) High risk: Patients meeting one or more of the following criteria at the time of randomization: (1) HLA-related (sibling) donor with at least one mismatch at one of the following 3 HLA-gene loci: HLA-A, -B, or -DR, (2) Haploidentical donor, (3) Unrelated donor with at least one mismatch at one of the following 4 HLA-gene loci: HLA-A, -B, -C or -DRB1, (4) Use of umbilical cord blood as stem cell source, (5) Use of *ex vivo* T-cell-depleted grafts [including *ex vivo* use of alemtuzumab], (6) Grade 2 or greater graft-versus-host disease (GVHD), requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).

Low risk: All patients not meeting the definition of high risk.

c) Letermovir 480 mg QD without cyclosporine, and letermovir 240 mg QD with concomitant cyclosporine. Subjects who received at least 1 dose of cyclosporine were classified as "cyclosporine."

The results of secondary efficacy endpoints etc. are shown in Table 38. The proportion of patients with clinically significant CMV infection through Week 14 post-transplant and the proportion of subjects with initiation of preemptive therapy through Week 14 or 24 post-transplant tended to be lower in the letermovir group than in the placebo group. The proportion of subjects with CMV end-organ disease was comparable between the letermovir and placebo groups, which was considered attributable to the initiation of preemptive therapy before the onset of CMV disease. The exploratory endpoint of the proportion of patients with documented CMV viremia through Week 14 or 24 post-transplant tended to be lower in the letermovir group than in the placebo group.

Based on the above, it was concluded that the efficacy of letermovir in the prophylaxis of CMV disease was demonstrated.

Table 38. Results of secondary efficacy endpoints etc. in Study 001 (FAS)

	Overall population		Japanese subgroup	
	Letermovir (N = 325)	Placebo (N = 170)	Letermovir (N = 24)	Placebo (N = 6)
"Clinically significant CMV infection" through Week 14 post-transplant[a)]	19.1 (62/325)	50.0 (85/170)	25.0 (6/24)	33.3 (2/6)
"CMV end-organ disease" through Week 24 post-transplant[b)]	1.5 (5/325)	1.8 (3/170)	0	0
"CMV end-organ disease" through Week 14 post-transplant[b)]	0.3 (1/325)	1.2 (2/170)	0	0
"Initiation of preemptive therapy" through Week 24 post-transplant[a)]	36.6 (119/325)	59.4 (101/170)	54.2 (13/24)	50.0 (3/6)
"Initiation of preemptive therapy" through Week 14 post-transplant[a)]	18.8 (61/325)	49.4 (84/170)	25.0 (6/24)	33.3 (2/6)
"Documented CMV viremia" through Week 24 post-transplant	57.2 (186/325)	72.9 (124/170)	79.2 (19/24)	100 (6/6)
"Documented CMV viremia" through Week 14 post-transplant	31.7 (103/325)	69.4 (118/170)	25.0 (6/24)	100 (6/6)

% (n/N)

a) Patients who discontinued the study before Week 24 post-transplant or had missing efficacy data at Week 24 post-transplant were considered as failures.

b) Investigator-reported cases of CMV end-organ disease (including suspected cases) were evaluated by an independent, blinded Clinical Adjudication Committee (CAC), and the cases of CAC-confirmed CMV end-organ disease were used for analyses.

(b) Japanese subgroup

In the Japanese subgroup, the proportions of subjects with clinically significant CMV infection through Week 24 post-transplant were 54.2% (13 of 24 subjects) in the letermovir group and 50.0% (3 of 6 subjects) in the placebo group, and the trend differed between the overall population and the Japanese subgroup.

However, given the following points, the efficacy of letermovir is expected also in Japanese allo-HSCT recipients, as in the overall population.

- Differences in preventive measures against CMV disease for allo-HSCT recipients, the distribution of CMV gB genotypes, the PK of letermovir, etc. between Japan and overseas are unlikely to have a significant impact on the efficacy of letermovir [see Section 6.R.1 and Section 7.R.1].
- In the Japanese subgroup, 3 subjects in the letermovir group and none in the placebo group discontinued the study for reasons unrelated to efficacy.[68)] Although these subjects were considered as failures for efficacy analyses, according to the pre-specified analysis plan, the discontinuations were considered to have a significant impact on the efficacy analyses as the number of subjects in the Japanese subgroup was small, i.e. 24 in the letermovir group and 6 in the placebo group.
- Among subjects who initiated preemptive therapy (excluding subjects who discontinued study drug or had missing efficacy data at Week 24 post-transplant), the proportion of subjects with detectable, but not quantifiable (<150 copies/mL) CMV DNA at the time of initiation of preemptive therapy was 61.5% (8 of 13 subjects) in the Japanese subgroup and 27.0% (34 of 126 subjects) in the overall population, and the proportion of subjects with CMV DNA >300 copies/mL at the time of initiation of preemptive therapy was 38.5% (5 of 13 subjects) and 59.5% (75 of 126 subjects), respectively. No common thresholds exist for the initiation of preemptive therapy in Japan and overseas, and the protocol for Study 001 specified the CMV DNA thresholds for the initiation of preemptive therapy, but stated that the determination of the need for preemptive therapy and the timing of initiation of preemptive therapy are left to the investigator's discretion. It seemed that the need for preemptive therapy was determined earlier in the Japanese subgroup than in the overall population in Study 001.
- The proportion of subjects with CMV viremia through Week 24 post-transplant was lower with letermovir: 100% (6 of 6 subjects) in the placebo group and 79.2% (19 of 24 subjects) in the letermovir group.
- In the Japanese subgroup, the proportion of subjects with clinically significant CMV infection through Week 14 post-transplant was lower in the letermovir group [25.0% (6 of 24 subjects)] than in the placebo group [33.3% (2 of 6 subjects)], and more failures occurred after the end of study treatment in the letermovir group. After the end of letermovir treatment, blood CMV DNA levels rose and the number of subjects with initiation of preemptive therapy increased in both the overall population and the Japanese subgroup, and there seemed no differences in the efficacy of letermovir after the end of treatment between the overall population and the Japanese subgroup.

PMDA's view:

Study 001 in allo-HSCT recipients demonstrated the superiority of letermovir over placebo in the primary endpoint of the proportion of patients with clinically significant CMV infection through Week 24 post-transplant. Given the following points, the results in the Japanese subgroup do not deny the efficacy of letermovir in Japanese patients, and the efficacy of letermovir in Japanese allo-HSCT recipients should be evaluated based on the results in the overall population. However, as there is limited clinical experience with letermovir in Japanese patients, it is necessary to collect post-marketing information on the efficacy of

[68)] One death due to cardiac failure (worsening of concomitant disease) (causally unrelated to study drug) and 2 cases of consent withdrawal

letermovir in Japanese allo-HSCT recipients and appropriately provide the obtained information to healthcare professionals in clinical practice.

- Differences in preventive measures against CMV disease for allo-HSCT recipients, the distribution of CMV gB genotypes, the PK of letermovir, etc. between Japan and overseas are unlikely to have a significant impact on the efficacy of letermovir [see Section 6.R.1 and Section 7.R.1], and at present, geographic differences in the susceptibility of CMV to letermovir are unlikely to exist [see Section 3.R.1]
- In the Japanese subgroup, the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant was higher in the letermovir group than in the placebo group, which was considered attributable to differences in physicians' judgment as to when and whether to initiate preemptive therapy, and the small number of evaluable subjects in the Japanese subgroup.
- The results of the exploratory endpoint of the proportion of subjects with documented CMV viremia through Week 24 post-transplant, etc. indicated that the efficacy of letermovir is expected.

7.R.2.2 Efficacy by route of administration

In a global phase III study (Study 001), as a rule, subjects were to receive the oral (tablet) formulation of study therapy, but the use of the IV formulation was allowed according to the subject's condition.[63)]

The applicant's explanation about the efficacy of letermovir by route of administration in Study 001:
The proportion of subjects with clinically significant CMV infection through Week 24 post-transplant by route of administration (subjects who received either the oral or IV formulation throughout the treatment period, or subjects who switched between the oral and IV formulations) is shown in Table 39. Among subjects who received the oral formulation only and subjects who switched between the oral and IV formulations, the proportion of subjects with clinically significant CMV infection was lower in the letermovir group than in the placebo group. On the other hand, all subjects who received the IV formulation only in the letermovir and placebo groups were classified as failures, of whom 7 subjects (excluding 1 subject in the placebo group) discontinued study drug (the treatment duration was 2 to 28 days; the reasons for discontinuations were an adverse event [5 subjects], the physician's decision [1 subject], and lack of efficacy [1 subject]). Such results were considered associated with the poor general condition of subjects who received the IV formulation only because they could not switch to the oral formulation. Since letermovir was effective in the prevention of CMV disease even in subjects who received the IV formulation for a certain period of time (up to 47 days) among subjects switched between the oral and IV formulations, the efficacy of letermovir administered by either route is expected.

Table 39. Proportion of subjects with clinically significant CMV infection through Week 24 post-transplant by route of administration (Study 001, FAS)[a)]

	Letermovir	Placebo
Oral formulation only	34.2 (80/234)	58.9 (76/129)
IV formulation only	100 (5/5)	100 (3/3)
Switched between oral and IV formulations	43.0 (37/86)	63.2 (24/38)

% (n/N)
a) Patients who discontinued the study before Week 24 post-transplant or had missing efficacy data at Week 24 post-transplant were considered as failures.

PMDA's view on the efficacy of letermovir by route of administration:
PMDA confirmed the efficacy of oral letermovir based on the results of Study 001 by route of administration.

All subjects who received the IV formulation only were classified as failures. However, the number of these subjects was very limited, and the IV formulation was to be given to only subjects who were unable to take oral therapy, as a rule, in Study 001.[63)] This suggests that the general condition of subjects who received the IV formulation only may have been different from that of subjects who were able to take oral therapy. Thus, it is difficult to reach a conclusion on the efficacy of the IV formulation based on these results. On the other hand, it is possible to conclude, based on the following points, that the efficacy of the IV formulation is expected. Meanwhile, it is necessary to collect post-marketing information on the efficacy of letermovir by route of administration, including the duration of treatment with the IV formulation, and appropriately provide any new finding to healthcare professionals in clinical practice.

- Following administration of letermovir 480 mg or letermovir 240 mg with concomitant cyclosporine in allo-HSCT recipients, the predicted letermovir $AUC_{0\text{-}24}$ at steady-state was higher after intravenous administration than oral administration [see Section 6.2.5.2].
- Among subjects who switched between the oral and IV formulations, the proportion of subjects with clinically significant CMV infection was lower in the letermovir group than in the placebo group, and some of these subjects received the IV formulation for a certain period of time.

7.R.2.3 Resistance

PMDA's view on letermovir-resistance mutations detected in Japanese and foreign clinical studies:
As discussed in Section 3.R.2, *in vitro* studies showed that amino acid substitutions in the UL56 subunit of the CMV DNA terminase complex may affect CMV susceptibility to letermovir. Among these substitutions, V236M substitution and a substitution at position C325 (C325W substitution) were identified in subjects who experienced CMV prophylaxis failure in clinical studies. However, as the available information on the association with decreased CMV susceptibility to letermovir/clinical efficacy is limited, it is important to collect post-marketing information on letermovir-resistance mutations, including the published literature, and provide any new finding to healthcare professionals in clinical practice.

7.R.3 Safety

Based on the following considerations, PMDA concluded that letermovir has acceptable safety in allo-HSCT recipients.

However, since there is limited clinical experience with letermovir in Japanese allo-HSCT recipients and the information on the safety of intravenous letermovir is limited, it is necessary to continue to collect such post-marketing information and appropriately provide it to healthcare professionals in clinical practice. It is also necessary to collect post-marketing information on the outcomes of pregnant women treated with letermovir and their babies and promptly provide any new finding to healthcare professionals in clinical practice.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3.1 Safety profile of letermovir

The applicant's explanation about the safety profile of letermovir:

A summary of safety in the overall population and the Japanese subgroup of a global phase III study (Study 001) is shown in Table 40.

Table 40. Summary of safety (Study 001, Treatment phase, Safety population)

	Overall population		Japanese subgroup	
	Letermovir (N = 373)	Placebo (N = 192)	Letermovir (N = 24)	Placebo (N = 11)
Adverse events	365 (97.9)	192 (100)	24 (100)	11 (100)
Adverse drug reactions[a)]	63 (16.9)	23 (12.0)	4 (16.7)	2 (18.2)
Severe adverse events[b)]	159 (42.6)	84 (43.8)	4 (16.7)	2 (18.2)
Serious adverse events	165 (44.2)	90 (46.9)	3 (12.5)	1 (9.1)
Adverse events leading to death	38 (10.2)	17 (8.9)	1 (4.2)	0
Adverse events leading to study drug discontinuation	72 (19.3)	98 (51.0)	5 (20.8)	5 (45.5)

n (%)

a) Adverse events assessed as related to study drug, b) Rated by the investigator as mild (signs or symptoms that are well-tolerated), moderate (discomfort causing some interference with usual activities), or severe (incapacitating with inability to do work or usual activities).

(a) Overall population

The main adverse events leading to death were acute myeloid leukaemia recurrent (7 subjects in the letermovir group, 3 subjects in the placebo group), graft versus host disease (5 subjects, 3 subjects), and septic shock (3 subjects, 3 subjects). A causal relationship to study drug was denied for all adverse events leading to death.

The main serious adverse events were graft versus host disease (37 subjects, 20 subjects), CMV infection (10 subjects, 13 subjects), acute myeloid leukaemia recurrent (11 subjects, 7 subjects), acute kidney injury (5 subjects, 9 subjects), pneumonia (8 subjects, 3 subjects), pyrexia (7 subjects, 4 subjects), and septic shock (4 subjects, 5 subjects). The serious adverse events reported by 3 subjects in the letermovir group (pancytopenia; thrombocytopenia; and delayed engraftment, 1 subject each) and 3 subjects in the placebo group (Bowen's disease; mental status changes; and acute kidney injury, 1 subject each) were assessed as causally related to study drug, and the outcome of the event reported by 1 subject in the letermovir group (pancytopenia) was reported as "unchanged" and the outcomes of other events were reported as "recovered/resolved."

The main adverse events leading to study drug discontinuation were CMV infection (23 subjects, 75 subjects), nausea (6 subjects, 2 subjects), and graft versus host disease (3 subjects, 2 subjects). The adverse events leading to study drug discontinuation reported by 18 subjects in the letermovir group (nausea [6 subjects]; vomiting [3 subjects]; abdominal pain [2 subjects]; anaemia; pancytopenia; thrombocytopenia; diarrhoea; hypersensitivity; delayed engraftment; blood creatinine increased; and confusional state [1 subject each] [some subjects were counted more than once because more than one event occurred]) and 7 subjects in the placebo group (nausea [2 subjects]; mouth ulceration; blood creatinine increased; Bowen's disease; mental status changes; and acute kidney injury [1 subject each]) were assessed as causally related to study drug, and the outcomes of the events reported by 1 subject in the letermovir group (pancytopenia) and 1 subject in the placebo group (blood

creatinine increased) were reported as "not recovered" and the outcomes of other events were reported as "recovered or recovering/resolving." The incidence of adverse events leading to study drug discontinuation was higher in the placebo group (51.0%) than in the letermovir group (19.3%), which is considered attributable to a higher incidence of CMV infection leading to study drug discontinuation in the placebo group (39.1% [75 of 192 subjects]) than in the letermovir group (6.2% [23 of 373 subjects]).

Adverse events that occurred in a ≥5% greater proportion of subjects in the letermovir group compared to the placebo group were cardiac disorders (SOC) (12.6% [47 of 373 subjects] in the letermovir group, 6.3% [12 of 192 subjects] in the placebo group) and hyperkalaemia (7.2% [27 of 373 subjects] in the letermovir group, 2.1% [4 of 192 subjects] in the placebo group). Since none of the events of hyperkalaemia were serious or led to study drug discontinuation and a causal relationship to study drug was denied for all cases, hyperkalaemia was not considered to pose a serious safety concern. Cardiac disorders are described in details in Section 7.R.3.2.

In Study 001, the dose of letermovir was 480 mg QD for subjects not on cyclosporine and 240 mg QD for subjects who received concomitant cyclosporine. Adverse events reported were largely similar, regardless of concomitant use of cyclosporine.

In the letermovir group of a foreign phase II study [Study 020, see Section 7.1], adverse events leading to death occurred in 2 subjects in the 60 mg group (acute graft versus host disease in intestine; and acute myeloid leukaemia, 1 subject each) and 1 subject in the 240 mg group (pneumonia), and serious adverse events occurred in 9 subjects in the 60 mg group (acute graft versus host disease in intestine [2 subjects], etc.), 12 subjects in the 120 mg group (pneumonia; and CMV infection [1 subject each], etc.), and 9 subjects in the 240 mg group (pneumonia; and acute graft versus host disease in intestine [2 subjects each], etc.). In a clinical study in patients with CMV viremia (Study 019),[69)] no adverse events leading to death were reported, and serious adverse events occurred in 1 subject in the letermovir 80 mg QD group (renal disorder and arteriovenous fistula aneurysm). A causal relationship to letermovir was denied for all fatal and serious adverse events reported in Studies 020 and 019.

Based on the above, the incidence of adverse events etc. in allo-HSCT recipients was largely similar between the letermovir and placebo groups, and letermovir is considered to have acceptable safety.

(b) Japanese subgroup
An adverse event leading to death occurred in 1 subject in the letermovir group (cardiac failure), but its causal relationship to study drug was denied.

69) Reference data, CTD 5.3.5.1.1. A foreign phase II study to evaluate the safety, efficacy, etc. of letermovir 40 mg BID or 80 mg QD in kidney or kidney/pancreas transplant recipients with CMV viremia under the conditions of a preemptive strategy.

Serious adverse events occurred in 3 subjects in the letermovir group (cardiac failure; bronchopulmonary aspergillosis; and platelet count decreased, 1 subject each) and 1 subject in the placebo group (adenoviral haemorrhagic cystitis), but a causal relationship to study drug was denied for all those events.

Adverse events leading to study drug discontinuation occurred in 5 subjects in the letermovir group (CMV infection [2 subjects]; vomiting; cardiac failure; and bronchopulmonary aspergillosis [1 subject each]) and 5 subjects in the placebo group (CMV infection [5 subjects]). The event reported by 1 subject in the letermovir group (vomiting) was assessed as causally related to study drug, and its outcome was reported as "recovered."

Based on the above, since the incidence of adverse events etc. in the Japanese subgroup was similar to that in the overall population, and there were no adverse events potentially unique to Japanese patients, there should be no particular safety concern about letermovir also in Japanese allo-HSCT recipients.

PMDA's view:
Based on the results of Study 001 etc., letermovir has acceptable safety in allo-HSCT recipients under the supervision of a physician with knowledge of and experience in hematological malignancies. According to the currently available data, no events potentially unique to Japanese patients have been reported. However, as there is limited clinical experience with letermovir in Japanese allo-HSCT recipients, it is necessary to collect post-marketing information on the safety of letermovir and appropriately provide the obtained information to healthcare professionals in clinical practice.

Cardiac effects of letermovir, the safety of intravenous letermovir, and the use of letermovir in pregnant women or in women who may possibly be pregnant are discussed in the following sections.

7.R.3.2 Cardiac disorder-related events

In Study 001, the incidence of cardiac disorder-related events[70)] was 12.6% (47 of 373 subjects) in the letermovir group, which was higher than 6.3% (12 of 192 subjects) in the placebo group.

The applicant's explanation about cardiac disorder-related events associated with letermovir:
In Study 001, the main cardiac disorder-related events were tachycardia (4.0% [15 of 373 subjects] in the letermovir group, 2.1% [4 of 192 subjects] in the placebo group), atrial fibrillation (3.5% [13 of 373 subjects], 1.0% [2 of 192 subjects]), cardiac failure (1.3% [5 of 373 subjects], 0 subjects], sinus tachycardia (1.1% [4 of 373 subjects], 1.6% [3 of 192 subjects]), atrial flutter (1.1% [4 of 373 subjects], 0 subjects), etc., most of which were mild or moderate in severity. Serious adverse events occurred in 6 subjects in the letermovir group (atrial fibrillation; atrial flutter; pericarditis; cardiac failure; arrhythmia; and sinus node dysfunction, 1 subject each) and 1 subject in the placebo group (cardiogenic shock [1 subject]), but a causal relationship to study drug was denied for all those events, and the outcomes of those events observed in the letermovir group were reported as "recovered," except for 1 case of cardiac failure (death). Except for the fatal event, no events led to study

70) Events falling under the MedDRA/J ver.19 SOC "Cardiac disorders."

drug discontinuation. Also with respect to vital signs (diastolic blood pressure, systolic blood pressure, heart rate) and ECG parameters (PR interval, QT interval, etc.), there was no trend uniquely associated with letermovir.

Based on the above, although the incidence of cardiac disorder-related events was higher in the letermovir group than in the placebo group in Study 001, most events were mild or moderate in severity, a causal relationship was denied for all those events, there was no trend uniquely associated with letermovir, and safety pharmacology, toxicity, and QT/QTc studies suggested no cardiac effects of letermovir [see Section 3.2, Section 5.2, and Section 6.2.4]. Thus, letermovir is unlikely to raise a cardiac safety concern.

PMDA's view:
The applicant's explanation (based on the occurrence of cardiac disorder-related events in Study 001, the results of non-clinical studies, the results of a QT/QTc study, etc., letermovir is unlikely to raise a cardiac safety concern) is acceptable. However, if a new finding about cardiac disorder-related events associated with letermovir becomes available after the launch, it should be provided appropriately to healthcare professionals in clinical practice.

7.R.3.3 Safety of intravenous letermovir

Following administration of letermovir 480 mg or letermovir 240 mg with concomitant cyclosporine in allo-HSCT recipients, the predicted letermovir $AUC_{0\text{-}24}$ at steady-state was higher after intravenous administration than oral administration [see Section 6.2.5.2]. The IV formulation of letermovir contains HP-β-CD as an excipient [see Section 2.3.1], and renal tubular epithelial cell vacuolation, hepatic enzyme elevations, etc. have been reported in repeated intravenous dose toxicity studies of HP-β-CD [see Section 2.R.1.2].

The applicant's explanation about the safety of intravenous letermovir:
In Study 001, as a rule, subjects were to receive the oral (tablet) formulation of study therapy, but the use of the IV formulation was allowed according to the subject's condition.[63)] A summary of safety after intravenous administration in this study is shown in Table 41. Although the incidence of adverse events was higher in the letermovir group than in the placebo group, the incidences of severe, serious, and adverse events leading to death and the incidence of adverse events leading to study drug discontinuation were lower in the letermovir group than in the placebo group. The main adverse events were graft versus host disease (11.1% [11 of 99 subjects] in the letermovir group, 16.7% [8 of 48 subjects] in the placebo group), febrile neutropenia (11.1% [11 of 99 subjects], 8.3% [4 of 48 subjects]), diarrhoea (11.1% [11 of 99 subjects], 8.3% [4 of 48 subjects]), pyrexia (10.1% [10 of 99 subjects], 10.4% [5 of 48 subjects]), and mucosal inflammation (7.1% [7 of 99 subjects], 14.6% [7 of 48 subjects]).

Adverse events at the administration site[71)] occurred in 3 subjects in the letermovir group (infusion site erythema; infusion site inflammation; infusion site pain; and infusion site swelling, 1 subject each [some subjects were counted more than once because more than one event occurred]), all of which were mild in

71) Events coded to the MedDRA/J ver.19 PTs containing the term "infusion site."

severity, and resolved. No adverse events at the administration site were reported in the placebo group. In phase I studies, adverse events at the administration site[72)] occurred in 36 of 92 subjects treated with intravenous letermovir (the IV formulation containing HP-β-CD) (pooled data). Of which, the events reported by 14 subjects (catheter site phlebitis [5 subjects]; catheter site pain; and catheter site related reaction [4 subjects each], etc.) were assessed as causally related to letermovir, but were mild in severity. Except for 1 case of infusion site reaction, all those events resolved.

Table 41. Summary of safety after intravenous administration (Study 001, Treatment phase, Safety Population)

	Letermovir (N = 99)	Placebo[c)] (N = 48)
Adverse events	84 (84.8)	35 (72.9)
Adverse drug reactions[a)]	9 (9.1)	2 (4.2)
Severe adverse events[b)]	22 (22.2)	16 (33.3)
Serious adverse events	16 (16.2)	13 (27.1)
Adverse events leading to death	3 (3.0)	3 (6.3)
Adverse events leading to study drug discontinuation	7 (7.1)	10 (20.8)

n (%)

a) Adverse events assessed as related to study drug, b) Rated by the investigator as mild (signs or symptoms that are well-tolerated), moderate (discomfort causing some interference with usual activities), or severe (incapacitating with inability to do work or usual activities), c) Saline or 5% dextrose solution was used.

Following intravenous administration, the occurrence of hepatic function- and renal function-related adverse events[73)] is shown in Table 42, and the proportion of subjects with Grade 3 or greater abnormal hepatic or renal laboratory changes[74)] is shown in Table 43. The occurrence of adverse events and abnormal laboratory changes after intravenous administration was largely similar between the letermovir and placebo groups.

72) Events coded to PTs containing the terms "infusion site," "injection site," "catheter site," " puncture site," or "application site" under SOC "General disorders and administration site conditions" of the MedDRA/J ver.19.

73) Events in the MedDRA/J ver.19 SMQs "Acute renal failure" or "Drug related hepatic disorders."

74) Grade 3 or greater abnormal laboratory changes were defined as follows: ALT increased, AST increased, and alkaline phosphatase increased ≥5 times the upper limit of normal; total bilirubin increased ≥2.6 times the upper limit of normal; blood urea nitrogen >31 mg/dL; creatinine ≥1.8 times the upper limit of normal or increase in creatinine ≥1.5 times of baseline

Table 42. Occurrence of hepatic function- and renal function-related adverse events (Study 001, Treatment phase, Safety population)

	Letermovir (N = 99)	Placebo (N = 48)
All hepatic function-related events	11 (11.1)	4 (8.3)
ALT increased	1 (1.0)	2 (4.2)
AST increased	1 (1.0)	2 (4.2)
Blood ALP increased	1 (1.0)	0
Blood bilirubin increased	2 (2.0)	1 (2.1)
Hepatic encephalopathy	1 (1.0)	0
Hepatic function abnormal	4 (4.0)	0
Hyperbilirubinaemia	3 (3.0)	1 (2.1)
Hypoalbuminaemia	1 (1.0)	2 (4.2)
International normalised ratio increased	0	1 (2.1)
Liver injury	1 (1.0)	0
Prothrombin time prolonged	1 (1.0)	0
All renal function-related events	6 (6.1)	3 (6.3)
Acute kidney injury	3 (3.0)	2 (4.2)
Protein urine present	0	1 (2.1)
Proteinuria	1 (1.0)	1 (2.1)
Renal failure	1 (1.0)	0
Renal impairment	1 (1.0)	0

n (%)

Table 43. Occurrence of Grade 3 or greater abnormal laboratory changes (Study 001, Treatment phase, Safety Population)

	Letermovir (N = 99)	Placebo (N = 48)
ALT	4 (4.0)	1 (2.1)
AST	3 (3.0)	1 (2.1)
ALP	1 (1.0)	0
Total bilirubin	4 (4.0)	6 (12.5)
Blood urea nitrogen	23 (23.2)	15 (31.3)
Creatinine	58 (58.6)	30 (62.5)

n (%)

Among subjects who switched between oral and intravenous letermovir (93 subjects in the letermovir group, 43 subjects in the placebo group), the incidences of adverse events before and after switching are shown in Table 44, and no apparent differences were observed before and after switching.

Table 44. Incidence of adverse events in subjects who switched between oral and IV letermovir (Study 001, Safety Population)

		Letermovir	Placebo
Switched from oral to IV letermovir	Before switching (oral)	84.8% (28/33)	85.7% (18/21)
	After switching (IV)	81.8% (27/33)	71.4% (15/21)
Switched from IV to oral letermovir	Before switching (IV)	85.0% (51/60)	72.7% (16/22)
	After switching (oral)	91.7% (55/60)	100% (22/22)

Based on the above, there should be no particular safety concern about intravenous letermovir, including renal and hepatic effects. However, a precautionary statement about the toxicity findings reported in the toxicity studies of HP-β-CD will be included in the package insert.

PMDA's view:

In Study 001, the occurrence of adverse events, laboratory abnormalities, etc. after intravenous administration was largely similar between letermovir and placebo. However, subjects received intravenous letermovir for a median of 12 days (range, 1-47 days) in Study 001, and it is envisaged that intravenous letermovir is administered for a longer period of time, according to the patient's condition, in clinical practice, compared to the clinical study. Nephrotoxicity etc. have been reported in the toxicity studies of HP-β-CD [see Section 2.R.1.2], and renal injury etc. may occur following prolonged treatment. Thus, the tablet formulation of

letermovir should be selected for patients who are able to take oral therapy. When intravenous letermovir is continued for a long period of time in patients who are not able to take oral therapy, etc., or intravenous letermovir is administered to patients with renal impairment, etc., such patients should be closely monitored by, e.g. renal function tests. Thus, healthcare professionals in clinical practice should be advised appropriately about these points. It is necessary to collect post-marketing information on the safety of intravenous letermovir and appropriately provide the obtained information to healthcare professionals in clinical practice.

7.R.3.4 Use in pregnant women or in women who may possibly be pregnant

Fetal skeletal abnormalities etc. were observed in embryo-fetal developmental toxicity studies of letermovir [see Section 5.R.2].

The applicant's explanation about the use of letermovir in pregnant women or in women who may possibly be pregnant:

In the present application, the intended population for letermovir is allo-HSCT recipients. Patients who plans to undergo transplantation need to receive cancer chemotherapy or systemic radiation therapy as a pre-conditioning regimen, and therefore pregnant female patients are not eligible for transplantation. In addition, generally, contraception is recommended for at least 2 years after HSCT (*Bone Marrow Transplant*. 2012;47:337-41). Thus, letermovir is unlikely to be used in pregnant women or in women who may possibly be pregnant. However, the possibility that letermovir is used in pregnant women or in women who may possibly be pregnant cannot be ruled out. In such cases, patients may be given an opportunity to use letermovir, provided that the package insert adequately alerts physicians to the risk of teratogenicity etc. associated with letermovir and then the expected therapeutic benefits are considered to outweigh the possible risks.

In a phase I study of letermovir, 1 subject tested positive for pregnancy after the last dose of letermovir, and the pregnancy outcome was elective abortion.

PMDA largely accepted the applicant's explanation. However, if letermovir may be used in pregnant women or in women who may possibly be pregnant, the following measures should be taken, considering the fetal effects of letermovir.

- Appropriately provide information including the results from embryo-fetal developmental toxicity studies of letermovir to healthcare professionals in clinical practice through informative materials etc., so as to help them weigh the expected benefits and potential risks of treatment with letermovir.
- Ensure information provision and alerting by developing informative materials, etc., so that prior to the use of letermovir in a pregnant woman or in a woman who may possibly be pregnant, the patient and her family are informed of and fully understand the risk of teratogenicity etc. associated with letermovir.
- Collect post-marketing information on the safety of letermovir in pregnant women and the outcome of their babies, in cooperation with obstetricians, promptly provide any important finding to healthcare professionals in clinical practice, and consider taking an appropriate action based on the obtained information.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of letermovir:

Allo-HSCT recipients are immunocompromised, which increases the risk for CMV disease due to the reactivation of latent CMV infection, etc. Actually, it has been reported that without prophylaxis, approximately 80% of CMV-seropositive patients experience CMV reactivation after allo-HSCT and that 20% to 35% of these patients develop CMV disease (*Hematol Oncol Clin North Am*. 2011;25:151-69). CMV disease may lead to a deteriorated general condition or death in HSCT recipients, and the Japanese and foreign clinical practice guidelines recommend preventive measures against CMV disease [see Section 7.R.1]. These clinical practice guidelines list prophylactic therapy and preemptive therapy for the prevention of CMV disease after allo-HSCT. In Japan, there are no drugs approved for the prophylaxis of CMV disease in allo-HSCT recipients, and preemptive therapy (initiation of treatment with anti-CMV agents after detection of CMV viremia, etc.) is mainly used at medical institutions. On the other hand, it has been reported that CMV reactivation is associated with an increased risk of overall mortality in the first year after hemopoietic stem cell transplantation, independent of the use of preemptive therapy, and with higher viral loads associated with higher risk of death (*Lancet Haematol*. 2016;3:e119-27). The currently approved anti-CMV agents, which are used for preemptive therapy, are associated with myelotoxicity, nephrotoxicity, etc. Thus, there is an unmet medical need for an effective and well-tolerated antiviral agent for the prophylaxis of CMV disease in allo-HSCT recipients.

A global phase III study (Study 001) demonstrated the efficacy of letermovir in the prevention of clinically significant CMV infection and its favorable safety in CMV-seropositive adult allo-HSCT recipients [see Section 7.R.2 and Section 7.R.3].

Letermovir is positioned as a drug for use in CMV prophylactic strategy. If letermovir can prevent CMV viremia, the use of preemptive therapy with currently approved anti-CMV agents, which are associated with adverse reactions, can be avoided. Also, the prognosis of allo-HSCT recipients may be improved. Thus, allo-HSCT recipients will benefit from letermovir.

PMDA asked the applicant to explain the use of letermovir in CMV-seronegative recipients of allo-HSCT from seropositive donors.

The applicant's explanation:

The Japanese clinical practice guideline states that 20% to 30% of CMV-seronegative recipients of allo-HSCT from seropositive donors develop primary CMV infection (Guideline of Japan Society for Hematopoietic Cell Transplantation, Volume 1, *Medicine and Drug Journal*. 2014;126-61). No clinical studies were conducted to evaluate the efficacy and safety of letermovir in these patients. However, taking account of the mechanism of action of letermovir, letermovir is expected to be effective and have acceptable safety in these patients, as in CMV-seropositive recipients. Thus, letermovir may be used in CMV-seronegative recipients of allo-HSCT from seropositive donors, provided that the physician fully understands the above background and then weighs the risks and benefits of treatment for each patient.

PMDA's view:
On the basis of the results from the global phase III study (Study 001), letermovir has efficacy in the prophylaxis of CMV disease in CMV-seropositive allo-HSCT recipients [see Section 7.R.2] and acceptable safety [see Section 7.R.3]. Taking account of the mechanism of action of letermovir, etc., a certain level of efficacy of letermovir will be expected and its safety will also be acceptable in CMV-seronegative recipients of allo-HSCT from seropositive donors. Given that CMV disease may lead to a serious outcome and is a serious complication affecting the prognosis in allo-HSCT recipients, it is clinically useful to allow the use of letermovir also in CMV-seronegative recipients of allo-HSCT from seropositive donors.

Based on the above, letermovir is clinically meaningful as a drug for the prophylaxis of CMV disease in allo-HSCT recipients.

However, since there is no information on the efficacy and safety of letermovir in CMV-seronegative recipients of allo-HSCT from seropositive donors, it is necessary to collect such post-marketing information and provide any new finding to healthcare professionals in clinical practice.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.5 Indication

The claimed indication for letermovir is "prevention of cytomegalovirus infection or cytomegalovirus disease in allogeneic hematopoietic stem cell transplant recipients."

PMDA's view on the indication of letermovir:
Based on the results of the primary and secondary efficacy endpoints, etc., in a global phase III study (Study 001), it was concluded that the efficacy of letermovir in the prophylaxis of CMV disease in Japanese allo-HSCT recipients is expected [see Section 7.R.2]. The results of Study 001 also demonstrated the efficacy of letermovir in the prevention of CMV viremia, which is a series of events that can progress to CMV disease. CMV viremia should also be part of "CMV disease" in the indication for letermovir. On the other hand, as the population for Study 001 was "recipients who were seropositive for CMV IgG antibodies (R+)," i.e. patients with latent CMV infection, the results of Study 001 did not prove the efficacy of letermovir in the prevention of "cytomegalovirus infection," which is part of the claimed indication. Thus, letermovir should be indicated for "prophylaxis of cytomegalovirus disease in allogeneic hematopoietic stem cell transplant recipients."

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

The applicant's explanation about the dosing rationale for letermovir:
In a global phase III study (Study 001), letermovir 480 mg QD without cyclosporine or letermovir 240 mg QD with concomitant cyclosporine [see Section 6.R.2] was to be administered orally or by intravenous infusion

over 60 minutes. Results demonstrated the efficacy of letermovir [see Section 7.R.2], and its safety was also considered acceptable, regardless of the route of administration and the concomitant use of cyclosporine [see Section 7.R.3]. The efficacy of letermovir in the Japanese subgroup is expected to be similar to that in the overall population, though the subgroup data from Study 001 are limited [see Section 7.R.2.1]. As there were no safety concerns specific to Japanese patients, letermovir was considered to have acceptable safety [see Section 7.R.3].

Thus, the proposed dose of letermovir is 480 mg orally or IV QD (240 mg when given with cyclosporine), and letermovir injection should be administered by intravenous infusion over 60 minutes.

PMDA's view:
Based on the efficacy [see Section 7.R.2] and safety [see Section 7.R.3] reviews and the following considerations, the proposed dosing regimen of 480 mg QD without cyclosporine or 240 mg QD with concomitant cyclosporine, administered orally (tablets) or by intravenous infusion over 60 minutes (injection), is acceptable.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.6.1 Intravenous administration

PMDA's view on intravenous administration of letermovir:
As discussed in Section 7.R.2.2 and Section 7.R.3.3, there are not sufficient data on intravenous letermovir in view of the number of subjects, the duration of treatment, etc. However, efficacy is expected from a clinical pharmacological point of view, and no serious safety concerns have been identified at present. Given that allo-HSCT recipients may be in poor general condition and that a certain proportion of patients are unable to take oral therapy, offering patients the option of intravenous letermovir is clinically meaningful. However, as discussed in Section 7.R.3.3, the tablet formulation of letermovir should be selected for patients who are able to take oral therapy.

7.R.6.2 Switching between oral and IV letermovir

The applicant's explanation about switching between oral and IV letermovir:
Following administration of letermovir 480 mg or letermovir 240 mg with concomitant cyclosporine in allo-HSCT recipients, the predicted $AUC_{0\text{-}24}$ of letermovir in plasma was lower after oral administration than intravenous administration [see Section 6.2.5.2]. In a global phase III study (Study 001), as a rule, subjects were to receive the oral (tablet) formulation of study therapy, and the use of the IV formulation was allowed according to the subject's condition. As a result, most subjects received the oral formulation, and the efficacy of letermovir was demonstrated [see Section 7.R.2.1]. Among subjects who switched between the oral and IV formulations, the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant was 43.0% (37 of 86 subjects) in the letermovir group, which was lower than 63.2% (24 of 38 subjects) in the placebo group. Thus, the efficacy of letermovir in subjects who switched between the oral and IV formulations was also demonstrated [see Section 7.R.2.2]. An assessment of safety in subjects who switched

between the oral and IV formulations (from the oral formulation to the IV formulation, or from the IV formulation to the oral formulation) showed no clear differences in the occurrence of adverse events before and after switching [see Section 7.R.3.3 Table 44].

Based on the above, it was concluded that the oral and IV formulations of letermovir may be switched according to the patient's condition.

PMDA's view:
The applicant's explanation (the oral and IV formulations of letermovir may be switched according to the patient's condition) is acceptable. However, as discussed in Section 7.R.2.2, Section 7.R.3.3, and Section 7.R.6.1, the package insert should advise that the tablet formulation should be selected for patients who are able to take oral therapy. It is also necessary to collect post-marketing information on the safety and efficacy of letermovir (by route of administration), and provide any new finding to healthcare professionals in clinical practice.

7.R.6.3 Duration of treatment

The applicant's explanation about the duration of treatment with letermovir:
It has been reported that without an appropriate preventive measure against CMV disease after allo-HSCT, CMV reactivation usually occurs within the first 24 weeks after transplantation, and that the risk of CMV reactivation is highest particularly during the first 14 weeks (approximately 100 days) after transplantation (*Bone Marrow Transplant.* 2007;40:125-36, *Lancet Infect Dis.* 2011;11:284-92, etc.). The Japanese clinical practice guideline recommends monitoring for CMV infection for ≥100 days after transplantation (Guideline of Japan Society for Hematopoietic Cell Transplantation, Volume 1, *Medicine and Drug Journal.* 2014;15-44). Thus, the treatment duration was through Week 14 post-transplant (approximately 100 days) in Study 001. The results of Study 001 demonstrated the efficacy of letermovir in the prophylaxis of CMV disease through Week 24 post-transplant, in patient treated with letermovir through Week 14 post-transplant.

On the other hand, the proportion of subjects with clinically significant CMV infection through Week 24 post-transplant was 37.5% in the letermovir group, which increased from the value at Week 14 post-transplant (19.1%). Failures occurred after the end of treatment with letermovir. The proportion of subjects with clinically significant CMV infection after the end of treatment by subgroup was 19.8% in the subgroup with graft versus host disease and 4.7% in the subgroup without graft versus host disease, 14.6% in the subgroup with the use of corticosteroids and 3.6% in the subgroup without the use of corticosteroids, and 17.6% in the high risk subgroup and 9.7% in the low risk subgroup (risk for CMV infection[66)] at baseline), indicating that the immunocompromised condition such as graft versus host disease and the use of corticosteroids and high risk for CMV infection are associated with an increased risk of developing CMV disease after the end of treatment. Thus, treatment with letermovir beyond Day 100 post-transplant may further reduce the incidence of CMV disease in these patients.

Based on the above, treatment with letermovir through Day 100 post-transplant is appropriate in light of the currently available information. Post-marketing information on the treatment duration will be collected, and a foreign clinical study is planned to evaluate the benefits of extending the duration of letermovir prophylaxis to 200 days.

PMDA's view:
Study 001 demonstrated the efficacy of letermovir in the prophylaxis of CMV disease through Week 24 post-transplant in allo-HSCT recipients treated with letermovir through Week 14 post-transplant. Allo-HSCT recipients are at the highest risk for developing CMV disease, especially during the first 100 days post-transplant. Given these findings, the package insert should recommend that the treatment duration should be through Day 100 post-transplant. On the other hand, the recovery of immune function after allo-HSCT varies between individual patients, and there were also subjects who experienced clinically significant CMV infection between Weeks 14 and 24 post-transplant in Study 001. CMV prophylaxis beyond Day 100 post-transplant may be needed according to the patient's condition in clinical practice. Thus, it is necessary to collect post-marketing information on safety and efficacy by treatment duration, determine a more appropriate treatment duration (including the data from a planned clinical study), and provide information to healthcare professionals in clinical practice, as appropriate.

7.R.7 Post-marketing investigations

The applicant is planning the following post-marketing surveillance of letermovir.
Use-results survey

- Objective: To detect/assess the information on safety and efficacy in clinical practice.
- Planned sample size: All patients treated with letermovir during the enrollment period
- Observation period: 1 year after the initiation of treatment with letermovir
- Survey period: 6 years (Enrollment period, 4 years)

PMDA considers that the following points should also be investigated in the post-marketing setting.

- Safety and efficacy by route of administration (especially, the safety and efficacy of intravenous letermovir)
- Safety and efficacy by treatment duration
- Safety of letermovir in pregnant women and the outcome of their babies
- Safety and efficacy in CMV-seronegative recipients of allo-HSCT from seropositive donors

Post-marketing information on letermovir susceptibility and resistance-associated mutations identified in clinical isolates from Japan and overseas should be collected from data sources including the published literature.

The above conclusion by PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that the efficacy of letermovir in the prophylaxis of CMV disease in adult allo-HSCT recipients is expected, and that letermovir has acceptable safety in view of its benefits. Letermovir is clinically meaningful because it can offer a new option for the prevention of CMV disease in allo-HSCT recipients.

PMDA has concluded that letermovir may be approved if letermovir is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 8, 2018

Products Submitted for Approval

Brand Name	(a) Prevymis Tablets 240 mg
	(b) Prevymis Intravenous Infusion 240 mg
Non-proprietary Name	Letermovir
Applicant	MSD K.K.
Date of Application	July 28, 2017

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the products submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in the Review Report (1) ("Section 7.R.2 Efficacy," "Section 7.R.4 Clinical positioning," "Section 7.R.5 Indication," and "Section 7.R.6 Dosage and administration").

PMDA also discussed the following points and took action as necessary.

1.1 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in "Section 7.R.3 Safety" in the Review Report (1), and made the following comment.

- Whether drugs that are administered early after allo-HSCT, such as letermovir, affect engraftment is important for assessing the usefulness of these drugs. It is recommended that healthcare professionals in clinical practice should be informed of whether letermovir affects engraftment.

Taking account of the comment from the expert advisors, PMDA obtained the following finding:

In a global phase III study (Study 001), the proportion of subjects who started study drug before engraftment[75)] and who achieved engraftment during the follow-up period was 95.4% (226 of 237 subjects) in the letermovir group and 91.3% (105 of 115 subjects) in the placebo group, and the median times to engraftment

[75)] In Study 001, engraftment was defined as documented absolute neutrophil counts ≥500/mm^3 on 3 consecutive days.

were 19 days (range, 7-49 days) and 18 days (range, 10-41 days), respectively. The proportion of subjects with engraftment and time to engraftment were similar between the letermovir and placebo groups.

PMDA instructed the applicant to provide the above information to healthcare professionals in clinical practice via informative materials, and the applicant agreed to take such action.

1.2 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in "Section 7.R.7 Post-marketing investigations" in the Review Report (1), and made the following comment.

- Letermovir was to be initiated any time from the day of transplantation until 28 days post-transplantation in the clinical study. However, the timing of initiation of letermovir prophylaxis may vary among individuals in clinical practice, because the period of increased risk for CMV disease differs from patient to patient, depending on the status of the primary disease, altered immune function due to treatment of chronic graft versus host disease, etc. It is necessary to collect post-marketing information on the timing of initiation of letermovir prophylaxis and the risk factors for CMV disease as well, and assess the effects of these factors on efficacy.

In view of the discussions presented in “Section 7.R.7 Post-marketing investigations” etc. in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA considers that post-marketing surveillance should also cover the following issues and that any new finding should appropriately be provided to healthcare professionals in clinical practice.

- Safety and efficacy by route of administration (especially, the safety and efficacy of intravenous letermovir)
- Safety and efficacy by treatment duration
- Efficacy by timing of initiation of prophylaxis
- Safety and efficacy by patient characteristics (e.g., the risk factors for CMV disease, conditioning regimen, immunosuppressive regimen)
- Safety of letermovir in pregnant women and the outcome of their babies
- Safety and efficacy in CMV-seronegative recipients of allo-HSCT from seropositive donors
- Safety of letermovir when co-administered with CYP2C8 substrates

Furthermore, it is necessary to collect information on genetic polymorphisms that influence the virulence of CMV (other than gB genotype), letermovir susceptibility and resistance mutations identified in clinical isolates from Japan and overseas, from data sources including the published literature.

PMDA instructed the applicant about the above points, and the applicant agreed to take such action.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for letermovir should include the safety and efficacy specifications presented in Table 45, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 46. The

applicant submitted an outline of use-results survey (draft) presented in Table 47.

Table 45. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	· Renal dysfunction associated with intravenous letermovir · Reproductive and developmental toxicity · Cardiac disorders	None
Efficacy specification		
None		

Table 46. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance · Use-results survey	· Disseminate data gathered during early post-marketing phase vigilance · Develop informative materials to be distributed to healthcare professionals · Develop informative materials to be distributed to patients

Table 47. Outline of use-results survey (draft)

Objective	To detect/assess information on safety and efficacy in clinical practice
Survey method	All-case surveillance
Population	Allo-HSCT recipients treated with letermovir
Survey period (Observation period)	6 years (1 year after initiation of treatment)
Planned sample size	All patients treated with letermovir during the enrollment period (Estimated enrollment, 450 patients)
Main survey items	Key survey items: renal dysfunction associated with intravenous letermovir, cardiac disorders, CMV disease (Yes/No) Others: patient characteristics, condition of transplantation, use of letermovir, concomitant medications/therapies, safety

1.3 Others

The expert advisors made the following comment on the intended population for letermovir:

As it is also envisaged that CMV is [redacted] etc., future development of letermovir for [redacted] is also expected.

Based on the comment from the expert advisors, PMDA considered that the development of a drug for [redacted] is important and that the applicant should consider the development of letermovir for [redacted], thus instructed the applicant accordingly. The applicant responded that [redacted].

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.3, CTD 5.3.5.1.5) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved after modifying the proposed indication and dosage and administration as shown below, with the following conditions. As the products are orphan drugs, the re-examination period is 10 years. The products are not classified as a biological product or a specified biological product, and the drug products and their drug substance are classified as powerful drugs.

Indication (Underline denotes change and strikethrough denotes omission from the proposed indication.)
Prophylaxis of ~~cytomegalovirus infection or~~ cytomegalovirus disease in allogeneic hematopoietic stem cell transplant recipients

Dosage and Administration (Underline denotes change from the proposed dosage and administration.)
Prevymis Tablets 240 mg
The usual adult dosage is 480 mg of letermovir administered orally once daily. If Prevymis is co-administered with cyclosporine, the dosage should be 240 mg of letermovir administered orally once daily.

Prevymis Intravenous Infusion 240 mg
The usual adult dosage is 480 mg of letermovir administered by intravenous infusion over approximately 60 minutes once daily. If Prevymis is co-administered with cyclosporine, the dosage should be 240 mg of letermovir administered by intravenous infusion over approximately 60 minutes once daily.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

List of Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
allo-HSCT	Allogeneic hematopoietic stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{inf}	AUC up to infinity
AUC_{last}	AUC up to the last time point with a measurable concentration after dosing
AUC_{0-t}	AUC up to t hours
BCRP	Breast cancer resistance protein
BID	bis in die
BSEP	Bile salt export pump
CC_{50}	50% cytotoxic concentration
CHO	Chinese hamster ovary
CL	Clearance
C_{max}	Maximum plasma concentration
CMV	Cytomegalovirus
C_t	Plasma concentration at t hours postdose
EC_{50}	50% effective concentration
ED_{50}, ED_{90}	50%/90% effective dose
efflux ratio	Basal-to-apical versus apical-to-basal ratio
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
gB	Glycoprotein B
GFP	Green fluorescent protein
GCV	Ganciclovir
HELF	Human embryonic lung fibroblast
HFF	Human foreskin fibroblast
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HP-β-CD	Hydroxypropyl-β-cyclodextrin
HPLC	High performance liquid chromatography
HSCT	Hematopoietic stem cell transplant
IgA/G/M	Immunoglobulin A/G/M
Ki	Enzyme-inhibitor constant
MDCK	Madin-Darby canine kidney
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MRC-5	Human fetal lung fibroblast
MRP	Multidrug resistance-associated protein
NHDF	Normal human dermal fibroblast
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically-based pharmacokinetic
PCR	Polymerase chain reaction
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QD	quaque die
t_{max}	Time to reach maximum plasma concentration
$t_{1/2}$	Elimination half-life

UGT	Uridine 5'-diphospho-glucuronosyltransferase
UL	Unique long
V_d	Volume of distribution