Report on the Deliberation Results

May 29, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Livtencity Tablets 200 mg
Non-proprietary Name	Maribavir (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 17, 2023

Results of Deliberation

At its meeting held on May 24, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

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

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a very limited number of Japanese subjects participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a certain number of patients have been accrued. The purposes of the survey are to identify the characteristics of these patients and to collect safety and efficacy data on the product without delay, thereby taking the necessary actions to facilitate the proper use of the product.

** Japanese Accepted Name (modified INN)*

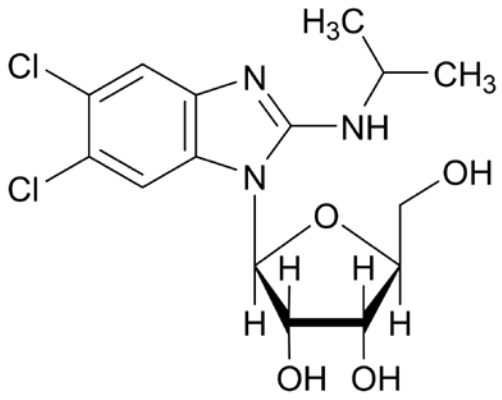
Review Report

May 15, 2024
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Livtencity Tablets 200 mg
Non-proprietary Name	Maribavir
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 17, 2023
Dosage Form/Strength	Film-coated tablets: Each tablet contains 200 mg of maribavir.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{15}H_{19}Cl_2N_3O_4$
Molecular weight: 376.24
Chemical name: 5,6-Dichloro-2-(propan-2-ylamino)-1-β-L-ribofuranosyl-1*H*-benzimidazole

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 537 of 2022 [R4 yaku]; PSEHB/PED Notification No. 0329-1 dated March 29, 2022, by the Pharmaceutical Evaluation 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 the product has efficacy in the treatment of cytomegalovirus disease refractory to existing anti-cytomegalovirus therapies in organ transplant recipients (including hematopoietic stem cell transplant recipients), and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

Cytomegalovirus disease refractory to existing anti-cytomegalovirus therapies in organ transplant recipients (including hematopoietic stem cell transplant recipients)

Dosage and Administration

The usual adult dosage is 400 mg of maribavir administered orally twice daily.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a very limited number of Japanese subjects participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a certain number of patients have been accrued. The purposes of the survey are to identify the characteristics of these patients and to collect safety and efficacy data on the product without delay, thereby taking the necessary actions to facilitate the proper use of the product.

Attachment

Review Report (1)

April 26, 2024

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 (PMDA).

Product Submitted for Approval

Brand Name	Livtencity Tablets 200 mg
Non-proprietary Name	Maribavir
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 17, 2023
Dosage Form/Strength	Film-coated tablets: Each tablet contains 200 mg of maribavir.
Proposed Indication	Treatment of cytomegalovirus disease in organ transplant recipients (including hematopoietic stem cell transplant recipients)

Proposed Dosage and Administration

The usual adult dosage is 400 mg of maribavir administered orally twice 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 fluid such as saliva secreted by CMV carriers (mostly latent infection), and the virus then remains latent in the body for life. Patients who have undergone hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT) are usually in an immunosuppressed state. CMV disease (including CMV viremia) resulting from reactivation of the latent CMV in such immunosuppressed patients or the transplanted organs or hematopoietic stem cells is associated with poor long-term outcome (*Antiviral Res*. 2006;71:154-163). If CMV disease is not promptly diagnosed and treated in SOT or HSCT recipients, they may experience fever, pneumonia, enteritis, hepatitis, retinitis, encephalitis, etc., leading to loss of the transplanted organs.

There are two types of treatment for CMV reactivation, primary CMV infection, or CMV reinfection in SOT or HSCT recipients: (a) preemptive treatment, whereby the recipients are regularly monitored for CMV infection by measurement of the level of CMV deoxyribonucleic acid (DNA) and anti-CMV medication is started when CMV infection is detected, and (b) anti-CMV medication for symptomatic CMV disease (HSCT-related CMV disease guideline). Currently, ganciclovir, valganciclovir, and foscarnet have been approved as anti-CMV drugs in Japan. However, the mechanism of action of all of these drugs is inhibition of viral DNA polymerase (pUL54), and *in vitro* results for cross-resistance and the development of resistance to the anti-CMV drugs in patients treated with the drugs have been reported (*Antiviral Res*. 2014;101:12-25, *J Med Virol*. 2008;80:1769-1775). The use of the existing anti-CMV drugs may result in serious adverse drug reactions (myelosuppression, etc. associated with the use of ganciclovir and valganciclovir; and renal disorder, electrolyte abnormalities, etc. associated with the use of foscarnet), which makes it difficult to administer the drugs at adequate dosages for adequate duration to some patients. Therefore, the development of new therapeutic drugs is awaited (*Transplantation*. 2016;100:e74-e80).

Maribavir is a novel antiviral drug discovered by the University of Michigan in the United States (US) and GlaxoSmithKline Plc. It inhibits the activity of the serine protein kinase pUL97, which is required in the processes of viral DNA replication of CMV, capsid formation, and release of viral capsid from the nucleus of the infected cells. Since maribavir exerts its effect through a different mechanism of action than the inhibition of DNA polymerase, it also shows antiviral activity against strains with mutations in pUL54 (*Antimicrob Agents Chemother*. 2002;46:2365-2372, *Herpesviridae*. 2010;1:4., etc.).

The development of maribavir was first initiated outside Japan for the treatment of CMV disease refractory to existing therapies (with or without genotypic resistance) in HSCT or SOT recipients. Additionally, the development of maribavir for the preemptive treatment of asymptomatic CMV viremia was conducted in HSCT or SOT recipients who have not previously been treated with any of the existing anti-CMV therapies (excluding treatment given before organ transplantation; the same applies hereinafter). However, the non-inferiority of maribavir in terms of efficacy to valganciclovir as the comparator could not be demonstrated in

HSCT recipients. In light of this situation, given that the results of a Japanese phase III study (Study 3001[1)]), a foreign phase III study (Study 303), and other studies have demonstrated the efficacy and safety of maribavir for the treatment of CMV disease refractory to existing anti-CMV therapies in Japanese HSCT or SOT recipients (with or without genotypic resistance), the applicant has submitted an application for marketing approval in Japan.

Outside Japan, maribavir has been approved in the US in November 2021 and in the European Union (EU) in November 2022 for the treatment of CMV disease refractory (with or without genotypic resistance) to existing anti-CMV therapies in organ transplant recipients (including HSCT recipients). As of February 2024, maribavir has been approved in 46 countries or regions.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to off-white solid. The determined general properties include description, solubility, hygroscopicity, melting point, thermal analysis (differential scanning calorimetry), acid dissociation constant (pKa), partition coefficient, and polymorphism. At least 30 types of crystalline forms have been identified in the drug substance. Only the [redacted] Form [redacted] was found to be formed during commercial-scale manufacture, and this crystalline form was confirmed to be stable at room temperature.

The chemical structure of the drug substance has been elucidated by ultraviolet-visible spectroscopy (UV/VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry (MS), elemental analysis, X-ray powder diffraction, and single-crystal X-ray structure analysis.

2.1.2 Manufacturing process

The drug substance is synthesized using the following starting materials: [redacted] and [redacted].

The quality control strategy has been designed based on the following investigations (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on quality risk assessment and the design-of-experiment method

[1)] Study 3001 included Japanese HSCT or SOT recipients with asymptomatic CMV viremia. Since the number of Japanese HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies was extremely limited, the efficacy of maribavir was evaluated in 3 HSCT or SOT recipients with refractory CMV disease enrolled in the Japanese phase III study. The safety was evaluated in all Japanese patients (N = 41) who received maribavir.

Table 1. Summary of control strategy for the drug substance

CQA	Control methods
Description	[redacted]
Identity	[redacted]
Related substances	[redacted]
[redacted]	[redacted]
Content	[redacted]
Water content	[redacted]
Residual solvents	[redacted]
Residue on ignition	[redacted]
Crystalline form	[redacted]
Microbial limit	[redacted]
Particle size	[redacted]

[redacted] of [redacted] and [redacted] of [redacted] have been defined as critical steps. [redacted], [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of the drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR and high performance liquid chromatography [HPLC]), purity (related substances [HPLC] and residual solvents (gas chromatography) [GC]), water content, residue on ignition, microbial limit, particle size, crystalline form, and assay (HPLC).

2.1.4 Stability of the drug substance

Table 2 shows the main stability studies performed on the drug substance. The results demonstrated the stability of the drug substance. Photostability testing showed that the drug substance was photostable.

Table 2. Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Low-density polyethylene bag (double layered) + polyethylene container	60 months
Accelerated		40°C	75% RH		6 months

In view of the above, a retest period of 60 months was proposed for the drug substance placed in a double-layered low-density polyethylene bag stored in a high-density polyethylene container at room temperature.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is an immediate-release film-coated tablet. Each tablet contains 200 mg of the drug substance. Excipients contained in the drug product are microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and [redacted].[2)]

[2)] Food Blue No. 1 Aluminum Lake, a designated food additive (dye), is used [redacted].

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: [redacted], [redacted], [redacted], lubricant mixing, tableting, film coating, packaging/labeling, testing, and storage. [redacted] and [redacted] have been defined as critical steps. In-process control parameters and control values have been established for the following steps: [redacted], [redacted], and [redacted].

The quality control strategy has been designed based on the following investigations (Table 3):

- Identification of CQAs
- Identification of critical material attributes based on the criticality analysis of material attributes in the manufacturing process and of manufacturing process parameters, which may affect CQAs

Table 3. Summary of control strategy for the drug product

CQA	Control methods
Description	[redacted]
Identity	[redacted]
Strength	[redacted]
Related substances	[redacted]
Uniformity of dosage units	[redacted]
Dissolution	[redacted]
Microbial limit	[redacted]

2.2.3 Control of the drug product

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

2.2.4 Stability of the drug product

Table 4 shows the main stability studies performed on the drug product. The results demonstrated the stability of the drug product. Photostability testing showed that the drug product was photostable.

Table 4. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	High-density polyethylene bottle + polypropylene cap with aluminum-laminated seal	36 months
Accelerated		40°C	75% RH		6 months

In view of the above, a shelf life of 36 months was proposed for the drug product filled in a high-density polyethylene bottle closed with a polypropylene cap with aluminum-laminated seal, stored at room temperature. The long-term testing will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and the drug product was controlled adequately.

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

The applicant submitted the following non-clinical pharmacology data on maribavir, in the form of results from studies on primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology. Unless otherwise specified, 50% effective concentration (EC_{50}) values used in this section are expressed as the mean.

3.1 Primary pharmacodynamics

3.1.1 Mechanism of action (Reference CTD 4.2.1.1-1 to 4.2.1.1-4)

To accurately investigate the mechanism of action of maribavir related to inhibition of the serine protein kinase pUL97, which is necessary for CMV replication,[3)] maribavir, ganciclovir (GCV), 1038U90 (concatemer maturation inhibitor), and foscarnet (FOS) were used to assess the mechanism of antiviral activity against CMV (AD169 strain) replication based on DNA levels, 72-hour inhibition of viral titer production, and CMV DNA concatemer maturation. The results suggested that maribavir inhibited DNA synthesis but did not affect concatemer maturation, even at concentrations that show antiviral activity (Table 5).

Table 5. Mechanism of antiviral activity against CMV replication

Indicator	EC_{50} (μmol/L)			
	Maribavir	GCV	1038U90	FOS
DNA level (exponential rate constant)	0.89	30	-	-
DNA level (DNA synthesis for 90 hours post-infection)	0.07	2	-	-
Viral titer (72 hours post-infection)	0.1	0.4	0.03	30
Concatemer maturation[a)]	27	>25	0.08	>500

-, no data.
Cell used: MRC-5 (human lung fibroblast cell line)
a) After allowing concatemers to accumulate in the cells by culturing CMV in the presence of 1038U90 (concatemer maturation inhibitor), 1038U90 was removed, and each test drug (including re-addition of 1038U90) was added to the cells. Then, the effect on concatemer maturation was assessed using viral titer as an indicator.

The relationship between the timing of maribavir addition and the inhibition of DNA synthesis was assessed. Addition of maribavir immediately after infection resulted in 95% inhibition of DNA synthesis up to 96 hours post-infection, whereas the inhibition of DNA synthesis was weaker when maribavir was added at 24 or 48 hours post-infection. The effect on the formation of DNA replication foci was investigated using BrdU uptake as an indicator. The formation of replication foci was inhibited immediately after the addition of maribavir.

Inhibitory activity against CMV DNA polymerase (pUL54) was investigated using uptake of [^{3}H]deoxynucleotide triphosphate (dATP, dCTP, dGTP, and dTTP) in the activated calf thymus DNA as an indicator. Maribavir did not inhibit CMV DNA polymerase.

In view of the above, maribavir had no direct effect on CMV DNA polymerase (pUL54), but was considered to exert its antiviral effect mainly by inhibiting the formation of the DNA replication foci of CMV through the inhibition of pUL97 and thereby blocking CMV DNA synthesis.

3) Maribavir was known to inhibit pUL97 in a screening study to explore pUL97 inhibitors before the start of development of maribavir.

3.1.2 *In vitro* antiviral activity

3.1.2.1 Antiviral activity against CMV (Reference CTD 4.2.1.1-1, 4.2.1.1-5 to 4.2.1.1-7, and 4.2.1.1-21)

The antiviral activity of maribavir was investigated in various types of cells infected with laboratory-established strains (AD169 and Towne) and clinical isolates of CMV. The EC_{50} against each CMV strain ranged from 0.03 to 0.31 μmol/L (mean, 0.11 μmol/L), and the EC_{50} of maribavir was lower than that of the comparator (GCV or FOS) (Table 6).

Table 6. Antiviral activity of maribavir against laboratory strains and clinical isolates

Viral strain used	Cell used	Test method	EC_{50} (μmol/L)	
			Maribavir	Comparator
AD169	MRC-5	DNA hybridization method	0.07	GCV: 2
Clinical isolates (10 strains)[a)]	MRC-5	DNA hybridization method	0.08	GCV: 0.59
AD169	MRC-5	DNA hybridization method	0.06	GCV: 0.15
	HEL	DNA hybridization method	0.03	GCV: 0.3
	MRHF	DNA hybridization method	0.2	GCV: 0.5
	MRC-5	DNA hybridization method	0.046	ND
		Inhibition of single-cycle viral replication	0.16	GCV: 0.9
				FOS: 42
AD169	MRC-5	DNA hybridization method	0.1	GCV: 0.53
		Inhibition of viral replication	0.1	GCV: 0.4
Towne		Inhibition of viral replication	0.6[b)]	GCV: 1.3[b)]
Clinical isolates (10 strains)[a)]		Plaque method	0.31	GCV: 3.9
AD169	MRC-5	ELISA	0.07	ND
AD169	MRC-5	DNA hybridization method	0.08	GCV: 0.31
AD169 (GCV-resistant variants[c)])		DNA hybridization method	0.1	GCV: 2.2

ND, no data; GCV, ganciclovir; FOS, foscarnet.

MRC-5, human lung fibroblast cell line; human embryonic lung cell line (HEL), human fetal lung-derived (fibroblast) cell line; MRHF, human foreskin fibroblast cell line.

a) US clinical isolate; b) EC_{90} was calculated in the study; c) 5 AD169 strains in which each amino acid substitution of M460V, H520Q, A594V, L595del, or A590A591C592R593del was introduced into pUL97.

Glycoprotein B (gB) of CMV, which is involved in viral entry into human host cells, is classified into 4 genotypes (gB1, gB2, gB3, and gB4) based on the amino acid sequence. The antiviral activity of maribavir against CMV clinical isolates was investigated by genotype (2 gB1 strains, 1 gB2 strain, 4 gB3 strains, and 1 gB4 strain) using the plaque method. The EC_{50} was 0.28 to 0.38 μmol/L (gB1), 0.51 μmol/L (gB2), 0.34 to 0.45 μmol/L (gB3), and 0.35 μmol/L (gB4), showing no differences in the antiviral activity of maribavir.

3.1.2.2 Antiviral activity against other viruses (Reference CTD 4.2.1.1-9 and 4.2.1.1-10)

The antiviral activity of maribavir against the following viruses was investigated: bovine viral diarrhea virus, respiratory syncytial virus, lymphocytic choriomeningitis virus, herpes simplex virus type 1, vaccinia virus, Tacaribe virus, rotavirus, severe acute respiratory syndrome-associated coronavirus, hepatitis B virus, human immunodeficiency virus, varicella zoster virus, and simian virus 40. Maribavir did not show antiviral activity against any of these viruses (EC_{50} >50 μmol/L).

3.1.2.3 Antiviral activity against strains resistant to other anti-CMV drugs (Reference CTD 4.2.1.1-21)

The viral activity of maribavir against CMV strains resistant to GCV, CDV, or ACV was investigated using the DNA hybridization method or the plaque method. Maribavir also showed antiviral activity against CMV

strains resistant to GCV, CDV, or ACV, with similar EC_{50} values to those against the wild-type AD169 strain (Table 7).

Table 7. Antiviral activity of maribavir against CMV strains resistant to other anti-CMV drugs

Strain	Mutant protein	Amino acid substitution	Phenotype	Test method	EC_{50} (μmol/L)		
					Maribavir	GCV	ACV
AD169	-	-	-	DNA hybridization method	0.08-0.09	0.23-0.31	ND
8805rec1	pUL97	M460V	GCV-resistant		0.03	1.7	ND
9330rec5	pUL97	H520Q	GCV-resistant		0.13	1.6	ND
8702rec2	pUL97	A594V	GCV-resistant		0.13	1.8	ND
9219rec7	pUL97	L595del	GCV-resistant		0.2	1.8	ND
XbaF.4	pUL97	A590A591C592 R593del	GCV-resistant		0.03	4.1	ND
GDG^{r}P53	pUL54	G987A	GCV-resistant		0.36	29	ND
AD169	-	-	-	Plaque method	2.2	4.5	52
1117^r	pUL54	K513D	GCV-resistant CDV-resistant Highly ACV-sensitive		5.3	10	9.2
ACV^{r}A	pUL54	M844T	GCV-resistant ACV-resistant		2.7	7.5	156
ACV^{r}B	pUL54	L802M	ACV-resistant		1.5	3.2	323
ACV^{r}C	pUL54	K513D	ACV-resistant		0.35	5.7	220

ND, no data; -, not applicable.

Maribavir has been reported to maintain antiviral activity against CMV variants that carry one or multiple mutations among 4 GCV-resistant amino acid substitutions (M460I, C592G, A594V, and L595S) in pUL97 and 5 GCV-, FOS-, or CDV-resistant amino acid substitutions (N408K, K513E, A809V, D981L982del, and A987G) in pUL54 (*J Clin Virol*. 2006;37:124-127).

Maribavir has also been reported to show antiviral activity against CMV variants carrying a letermovir (LTV)[4)]-resistant amino acid substitution (V236M) in the CMV terminase complex (pUL56) (*Antiviral Res*. 2018;157:128-133).

3.1.3 Resistance profile

3.1.3.1 Amino acid substitutions that reduce the antiviral activity of maribavir (Reference CTD 4.2.1.1-8 and 4.2.1.1-11, Reference CTD 4.3: *Antimicrob Agents Chemother*. 2013;57:3375-3379, *Antiviral Res*. 2012;95:88-92, *Antiviral Res*. 2019;172:104616., etc.)

Amino acid substitutions that reduce the antiviral activity of maribavir have been reported in several publications. Table 8 shows an outline of these amino acid substitutions. The catalytic domain of pUL97 is composed of 11 main conserved regions. Of these, Domain I (amino acid residues 337-345) contains an ATP binding site (P-loop), Domain VII (amino acid residues 481-483) contains a phosphotransfer domain, and Domain IX (amino acid residues 553-557) contains a substrate recognition site. Many of the amino acid substitutions in pUL97 that affect the antiviral activity of maribavir were found to be located in or near these regions. Amino acid substitutions in pUL27 also reduce the antiviral activity of maribavir, although pUL27 is not the target molecule of maribavir and its biological function has not been fully elucidated. The reduction in

4) A drug that prevents the development of CMV disease.

the antiviral activity of maribavir in the presence of amino acid substitutions in both pUL97 and pUL27 was greater than when amino acid substitutions were only present in either pUL97 or pUL27.

Table 8. Maribavir-resistant amino acid substitutions reported

Amino acid substitution	EC_{50} (µmol/L)	EC_{50} fold-increase[a)]	Source
pUL97 mutations			
K335del	36.5	304.2	I
L337M	0.37-0.39	3.4-3.5	II
F342S	2.2	18.3	I
F342Y	0.51	4.6	III
V353A	1.22-2.0	10.2-15.5	I, II, IV, V
V356G	12.98	108.2	I
L397R	2.7->28	33.8->200	IV, V, VI, VII
T409M	10.5	75.0	IV, V
H411L	7.6	69.1	V
H411N	1	9.1	V
H411Y	1.3	11.8	V
D456N	37	284.6	VIII
V466G	38.51	320.9	I
C480F	28	233.3	IX
C480R	32.4	249.2	VIII
P521L	51.40-53.35	428.3-444.6	I
Y617del	49.7	382.3	VIII
F342Y + H411Y	6.4	58.2	III
V353A + H411L	25	227.3	V
V353A + H411Y	18	163.6	V
pUL27 mutations			
Del (1-497)	0.35	3.2	X
E22stop	0.19	2.0	XI
W153R	0.16	1.7	XI
L193F	0.24	2.5	XI
218delC	0.23	2.4	XI
R233S	0.2-0.52	1.8-5.2	II, X
A269T	0.19	2.0	XI
301-311del + A311 flame shift, deletion	0.29	3.1	XI
V353E	0.2	2.1	XI
W362R	0.21	1.9	X
L426F	0.21	2.2	XI
R448P	0.17	1.5	II
D534Y	0.15	1.4	II
A406V + C415STOP	0.39	3.5	X
Combination of pUL27 and pUL97 mutations			
R233S (pUL27) + L337M (pUL97)	0.79	7.2	II
R233S (pUL27) + V353A (pUL97)	2.94	27	II

a) Compared to EC_{50} against the wild-type strain used in each source.

Sources:

I) *Antimicrob Agents Chemother*. 2013;57:3375-3379, II) *Antiviral Res*. 2012;95:88-92, III) *Antiviral Res*. 2019;172:104616, IV) *J Infect Dis*. 2007;196:91-94, V) *J Virol*. 2008;82:246-253, VI) *Antimicrob Agents Chemother*. 2002;46:2365-2372, VII) *J Clin Virol*. 2006;37:124-127, VIII) *Antimicrob Agents Chemother*. 2014;58:274-278, IX) *J Infect Dis*. 2022;226:576-584, X) *J Virol*. 2004;78:7124-7130, XI) *Antimicrob Agents Chemother*. 2009;53:81-85.

3.1.3.2 Cross-resistance to other anti-CMV drugs (Reference CTD4.3: *Antimicrob Agents Chemother*. 2013;57:3375-3379, *Antiviral Res*. 2019;172:104616, *J Infect Dis*. 2022;226:576-584, *Antimicrob Agents Chemother*. 2014;58:274-278)

Amino acid substitutions in pUL54 showing resistance to GCV, FOS, and CDV have been confirmed not to affect the antiviral activity of maribavir [see Section 3.1.2.3]. In contrast, amino acid substitutions F342S, F342Y, V356G, D456N, V466G, C480F, C480R, P521L, and Y617del in pUL97, which have been confirmed to show resistance to maribavir [see Section 3.1.4.1], have been reported to show cross-resistance between

GCV and maribavir, because pUL97 is involved in the intracellular conversion of GCV to its active form. Table 9 shows an outline of the cross-resistance due to these amino acid substitutions.

Table 9. Amino acid substitutions with cross-resistance between maribavir and GCV, and antiviral activity

Mutant protein	Amino acid substitution	Maribavir		GCV		Source
		EC_{50} (μmol/L)	EC_{50} fold-increase[a)]	EC_{50} (μmol/L)	EC_{50} fold-increase[a)]	
pUL97	F342S	2.20	18.3	7.83	7.8	I
	V356G	12.98	108.2	5.55	5.4	
	V466G[b)]	38.51	320.9	11.44	11.3	
	P521L[b)]	51.40-53.35	428.3-444.6	17.53-17.63	17.4-17.5	
	F342Y	0.51	4.5	7.2	6.0	II
	C480F	28	224	3.10	2.3	III
	D456N[b)]	37	284.6	13.4	11.2	IV
	C480R[b)]	32.4	249.2	10.3	8.6	
	Y617del[b)]	49.7	382.3	11.2	9.3	

-, not applicable.

a) Compared to EC_{50} against the wild-type strain used in each source; b) Viral replication ability is decreased.

Sources:

I) *Antimicrob Agents Chemother*. 2013;57:3375-3379, II) *Antiviral Res*. 2019;172:104616, III) *J Infect Dis*. 2022;226:576-584, IV) *Antimicrob Agents Chemother*. 2014;58:274-278.

3.1.3.3 Amino acid substitutions observed after maribavir administration in each clinical study (CTD 5.3.5.4-1-03, 5.3.5.4-2-01, and 5.3.5.4-3)

Amino acid sequencing of CMV pUL97 was performed using specimens isolated from subjects in foreign phase II and phase III studies (Studies 202, 203, 303, and 302) and a Japanese phase III study (Study 3001). Known maribavir-resistant amino acid substitutions were detected after maribavir administration (Table 10). Amino acid substitutions related to maribavir resistance were not detected in the pUL27 region, which was also included in the sequencing analysis.

Table 10. Maribavir-resistant mutations observed after maribavir administration in clinical studies

Study (No. of subjects analyzed)	Amino acid substitutions (No. of subjects)[b)]
Studies 202 and 203 (N = 68)[a)]	T409M (19 subjects), C480F (9 subjects), H411Y (4 subjects), T409M + C480F (2 subjects), F342Y + H411Y (1 subject)
Study 3001 (N = 41)	C480F (2 subjects), T409M, T409M + H411Y, T409M + C480F (1 subject each)
Study 303 (N = 234)	T409M (15 subjects), H411Y (12 subjects), C480F (11 subjects), T409M + H411Y (8 subjects), T409M + C480F (6 subjects), H411Y + C480F (2 subjects), F342Y, H411N, F342Y + H411Y, H411N + C480F, F342Y + T409M + H411N, H411L/Y + C480F (1 subject each)
Study 302 (N = 273)	T409M (12 subjects), H411Y (6 subjects), T409M + H411Y (5 subjects), T409M + C480F (1 subject)

a) Resistant mutations observed in relapsed subjects after resolution of CMV viremia and non-responders were combined.

b) F342Y and C480F have been reported to show cross-resistance to GCV in addition to maribavir in publications [see Section 3.1.3.2].

In Studies 3001, 303, and 302, mutations resistant to other anti-CMV drugs that do not affect the sensitivity to maribavir were also investigated. Resistant mutations after maribavir administration were only observed in Study 303 (Table 11).

Table 11. Mutations resistant to other anti-CMV drugs observed after maribavir administration in clinical studies

Study (No. of subjects analyzed)	Drugs to which mutations show resistance	Mutant protein	Amino acid substitutions (No. of subjects)
Study 303 (N = 234)	GCV	pUL97	A594V (3 subjects), M460V (2 subjects), H520Q, L595S, E596G, C603W (1 subject each)
	FOS	pUL54	S290R, V715M (1 subject each)
	CDV, GCV		N408D, L501I, T503I, K513N, L516P, P522T, A987G (1 subject each)
	CDV, FOS, GCV		C590F, L773V, S290R + G841A (1 subject each)
	FOS, GCV	pUL97 + pUL54	L595F (pUL97) + G841S (pUL54) (1 subject)

The applicant explained as follows: In Study 302 in HSCT recipients with asymptomatic CMV viremia who had never been treated with existing anti-CMV therapies, mutations resistant to other anti-CMV drugs caused by maribavir use were not detected. The resistant mutations observed in Study 303 were therefore mutations that had been caused by other anti-CMV drugs that had been used before the clinical trial participation, which had not been detected at baseline but were detected after a certain period.

3.1.4 *In vivo* antiviral activity (Reference CTD 4.3: *Antimicrob Agents Chemother*. 2004;48:1749-1755)

CMV does not directly infect animals other than humans, and maribavir has weak or no antiviral activity against cytomegaloviruses derived from other animal species.[5)] Therefore, a retinal tissue infection model and a thymus/liver tissue infection model were prepared by transplanting human fetal retinal and thymus/liver tissues into the anterior chamber of the eye and the kidney capsule of severe combined immunodeficient (SCID) mice, respectively. They were inoculated with CMV (Toledo strain; 2,000-7,500 PFU (plaque-forming units) for retinal tissue transplantation and 2,000-9,000 PFU for thymus/liver tissue transplantation) at 6 to 14 weeks post-transplantation. Maribavir, GCV, or the vehicle (0.5% methylcellulose solution)[6)] was administered to the tissue infection models for 28 days starting at 24 hours after the viral inoculation, and the viral titers in the eye and thymus/liver biopsy tissues were investigated by plaque assay. In both models, the decrease in viral titer was similar in the GCV and the maribavir groups compared to the vehicle control group.

3.1.5 Cytotoxicity (Reference CTD 4.2.1.1-19 and 4.2.1.1-20)

To evaluate the risk of hematotoxicity caused by maribavir, cytotoxicity was assessed in human myeloid precursor-derived cells (colony-forming unit-granulocyte/macrophage [CFU-GM] and burst-forming unit-erythroid cells [BFU-E]), human T-cell leukemia cell lines (MOLT-4, CEM, and CEM-CD^{4+} cells), and a human B-cell leukemia cell line (IM9), based on the EC_{50} of each type of cell as an indicator. The EC_{50} of maribavir was 90 μmol/L (CFU-GM), 88 μmol/L (BFU-E), 35 μmol/L (MOLT-4), 44 μmol/L (CEM), 76 μmol/L (CEM-CD^{4+}), and 43 μmol/L (IM9), and these values were higher than the concentrations at which its antiviral activity is observed. In the studies that investigated the antiviral activity of maribavir [see Section

5) The *in vitro* antiviral activity (EC_{50}) of maribavir against cytomegaloviruses (MCMV, RCMV, GPCMV, and RhCMV), which infect mice, rats, guinea pigs, and rhesus monkeys, respectively, was >11, >11, >53, and 48 μmol/L, respectively (*Antimicrob Agents Chemother*. 2003;47:2186-2192).

6) Dosage regimens of the test drugs in each infection model:
- Retinal tissue infection model: Maribavir (25 or 75 mg/kg twice daily for 14 days and once daily for the subsequent 14 days, orally), GCV (33 mg/kg once daily, intraperitoneally), and the vehicle (twice daily for 14 days and once daily for the subsequent 14 days, orally).
- Thymus/liver tissue infection model: Maribavir (33 or 100 mg/kg twice daily, orally), GCV (33 mg/kg once daily, intraperitoneally), and the vehicle (twice daily, orally).

3.1.2.1], cytotoxicity against MRC-5, HEL, and MRHF cells was also investigated. No clear cytotoxicity was observed at concentrations at which the antiviral activity of maribavir was seen.

3.2 Secondary pharmacodynamics

3.2.1 Effects on the metabolic system, allergy and inflammation, and the gastrointestinal system (Reference CTD 4.2.1.2-1)

The off-target effects of maribavir were investigated *in vitro* or *in vivo* for the following systems: metabolic system (cholesterol regulatory effect, lipoprotein regulatory effect, blood glucose, sodium excretion, potassium excretion, and diuresis), allergy and inflammation (anti-inflammatory effect, anti-allergic effect, H_1 histamine receptor antagonistic effect, platelet-activating factor-induced aggregation, tracheal contraction, leukotriene D_4 receptor antagonistic effect, bradykinin 2 receptor antagonistic effect, and substance P receptor antagonistic effect), and the gastrointestinal system (stress-induced gastric ulcer, ethanol-induced gastric ulcer, gastric acid secretion, serotonin receptor antagonistic effect, electroshock-induced contractile stimulation, and cholecystokinin receptor antagonistic effect). Maribavir did not inhibit or stimulate any of the above systems at the doses or concentrations studied.

3.2.2 Effects on autonomic nervous system (Reference CTD 4.2.1.2-2)

Effects on cholinergic muscarinic receptors and histaminergic H_1 receptors were investigated using guinea pig isolated ileum. Both acetylcholine- and histamine-induced contraction of the ileal longitudinal muscle was inhibited in the presence of maribavir (10 μmol/L). The effect on α_1-adrenergic receptors was investigated using rabbit isolated aorta. No effects on noradrenaline-induced contraction of the aorta were observed in the presence of maribavir (10 μmol/L). In these studies, maribavir concentrations were 6.7 to 9.1 times the human exposure (unbound C_{max} [μg/mL],[7)] 0.402 [overall population] or 0.582 [Japanese patient population]).

Although clinical signs (decreased activity and hypothermia) possibly related to anticholinergic action[8)] or antihistaminic action[9)] were observed in a non-clinical safety pharmacology study and single- and repeated-dose toxicity studies in mice [see Sections 3.3 and 5.2], the applicant considered that these findings are unlikely to raise clinical concerns for the following reasons:

- The clinical signs in the non-clinical safety pharmacology study and the single- and repeated-dose toxicity studies in mice were observed at doses leading to death, and were considered to have been caused by weak anticholinergic or antihistaminic effects that could occur at higher concentrations than the human exposure.
- According to the results of repeated-dose toxicity studies in rats and monkeys [see Section 5.2], there were no findings related to reduced gut motility.
- In clinical studies, no adverse drug reactions related to anticholinergic or antihistaminic effects were

7) Unbound C_{max} was calculated by multiplying the steady-state C_{max} following twice daily multiple-dose administration of maribavir 400 mg in CMV-infected organ transplantation patients (overall population and Japanese population) estimated using a PPK model (20.1 μg/mL in the overall population and 29.1 μg/mL in the Japanese population) by the plasma protein-unbound fraction of maribavir in humans (2%; CTD 4.2.2.3-6).

8) Hypothermia, tachycardia, reduced gut motility, constipation, vomiting, and mydriasis, etc. [Stat Pearls. Anticholinergic Medications: https://www.ncbi.nlm.nih.gov/books/NBK555893/ (last accessed on April 1, 2024)]

9) Sedation, gastrointestinal symptoms (diarrhea or constipation), and dry mouth, etc. [Stat Pearls. Antihistamines: https://www.ncbi.nlm.nih.gov/books/NBK538188/ (last accessed on April 1, 2024)]

observed.

3.3 Safety pharmacology (Reference CTD 4.2.1.3.1 to 4.2.1.3.3)

Safety pharmacology studies, excluding the human ether-a-go-go related gene (hERG) study, were conducted as non-GLP-compliant studies before enforcement of "Guideline for safety pharmacology" (PMSB/ELD Notification No. 902 dated June 21, 2001, by the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare). In these studies, the effect of maribavir on the central nervous system, cardiovascular system, and respiratory system was investigated (Table 12).

Table 12. Summary of safety pharmacology studies

Organ system evaluated	Test system	Evaluation items/methods, etc.	Dose	Route of administration	Findings
Central nervous system	CD-1 mice (4 males/dose)	Body weight, rectal temperature, respiratory rate, reflex behavior, analgesic effect (Irwin method)	Maribavir 250, 500, 1,000 mg/kg	p.o.	250 mg/kg: Decreased activity, hypothermia, blepharospasm, and fluctuation in respiratory rate 500 mg/kg: Ataxic gait, coarse tremor, diarrhea, hypotonia, and disappearance of reflex behavior 1,000 mg/kg: gasping respiration and death preceded by cyanosis Non observed effect level: <250 mg/kg
Cardiovascular system	hERG-transfected human embryonic kidney (HEK) 293 cells	hERG current (whole-cell patch clamp method)	Maribavir 0, 58.7, 188.6, 568.5, 1,254.0 μg/mL	*In vitro*	No inhibition up to 1,254.0 μg/mL
	Beagle dogs (under anesthesia; 3 males/dose)	Arterial blood pressure, heart rate, autonomic nervous system function[a)]	Maribavir 0, 43 (cumulative)[b)] mg/kg	i.v. (bolus)	30 mg/kg: Transiently increased heart rate No effects on the autonomic nervous system function Non observed effect level: 10 mg/kg
Respiratory system		Respiratory rate, minute volume			10 and 30 mg/kg: Transiently increased respiratory rate and respiratory volume Non observed effect level: 3 mg/kg

a) At the cumulative dose of 43 mg/kg, changes in blood pressure due to carotid artery occlusion and changes in heart rate due to vagus nerve stimulation were assessed.
b) Dose escalation of 3, 10, and 30 mg/kg mg at 30-minute intervals

The applicant provided the following discussion on the effect of maribavir on the central nervous system, cardiovascular system, and respiratory system, in view of the results of GLP-compliant toxicity studies and clinical studies:

Concerning the effect on the central nervous system, decreased activity, collapse, and death were observed at doses ≥500 mg/kg/day, and also convulsions, abnormal vocalization, and ataxic gait at 1000 mg/kg/day in the single-dose toxicity study in mice. These findings were considered to be secondary effects observed at doses leading to death. In repeated-dose toxicity studies in mice, rats, and monkeys [see Section 5.2], there were no effects on clinical signs/behavior. In phase II clinical studies (Studies 202 and 203) and phase III clinical studies (Studies 3001, 302, and 303), the common adverse drug reactions classified under the system organ class (SOC) "nervous system disorders" were taste disorder (taste disturbance) and headache. However, most of these events resolved during or after treatment and were mild or moderate.

Concerning the effect on the cardiovascular system, no effects on electrocardiogram (ECG) parameters were observed following maribavir administration in repeated-dose toxicity studies in monkeys [see Section 5.2]. Maribavir also did not show a risk of QT prolongation in the assessment study of QT and corrected QT interval (QTc) (Study 1263-108). Although hypotension (2 subjects), and hypertension, hot flushes, and sinus tachycardia (1 subject each) were reported as cardiovascular adverse drug reactions in Studies 202, 203, 3001, 302, and 303, all of these events resolved and were mild or moderate, except for hypotension in 1 subject.

Concerning the effect on the respiratory system, gasping respiration and labored respiration were observed at 1,000 mg/kg/day in the single-dose toxicity study in mice and 1,500 mg/kg/day in the single-dose toxicity study in rats. Both findings were considered to be secondary effects observed at doses leading to death. In repeated-dose toxicity studies in mice, rats, and monkeys [see Section 5.2], there were no effects on the respiratory system. Although dry throat and cough (1 subject each) were reported as respiratory adverse drug reactions in Studies 202, 203, 3001, 302, and 303, both events resolved and were mild.

In view of the above, the clinical use of maribavir at the proposed dosage and administration is unlikely to raise safety concerns due to its effect on the central nervous system, cardiovascular system, or respiratory system.

3.4 Pharmacodynamic interactions (Reference CTD 4.2.1.1-11 and 4.2.1.1-13)

The combined effect of maribavir with each of the other anti-CMV drugs (CDV, FOS, GCV, or LTV) was investigated[10)] using the checkerboard titration method with a human retinal pigment epithelial cell line expressing platelet-derived growth factor α receptor (ARPEp) infected with various resistant CMV strains.[11)] Regardless of the resistant mutations, maribavir was determined to be antagonistic to GCV and additive with the other anti-CMV drugs. The combined effect of maribavir and each of the other anti-CMV drugs (ACV, FOS, GCV, or CDV) was also investigated[12)] with MRC-5 cells infected with the AD169 strain. Maribavir was determined to be additive with ACV, FOS, or GCV, and synergistic with CDV.

The applicant's explanation about the pharmacodynamic interaction with GCV:
GCV needs to be phosphorylated by pUL97 to exert its anti-CMV effect, and maribavir inhibits pUL97. Therefore, maribavir is considered to be antagonistic to GCV when these drugs are concomitantly used.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activity of maribavir against CMV and profile of resistance to maribavir

The applicant's explanation:
Although the antiviral activity of maribavir has not been investigated using clinical isolates obtained in Japan, maribavir can be expected to show similar antiviral activity against Japanese clinical isolates to that against laboratory-established strains and US clinical isolates for the following reasons:

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10) The MacSynergy TM II program was used for the assessment (*Antiviral Res.* 1990;14:181-205).
11) Wild-type strain, pUL97 T409M strain, and pUL97 H411Y strain (resistant to maribavir), pUL56 V236M strain (resistant to LTV), and pUL54 D981L982del strain (resistant to CDV, FOS, and GCV).
12) The method of Elion G.B., et al. was used for the assessment (*J Biol Chem.* 1995;208:477-488).

- None of the pUL97 mutations reported with CMV strains isolated in Japan have been reported to reduce the sensitivity to maribavir to date (*Sci Rep*. 2021;11:13676, *BMC Infect Dis*. 2022;22:568, etc.)
- In the Japanese phase III study (Study 3001), known maribavir-resistant mutations were not detected at baseline, and the types and frequency of maribavir-resistant mutations detected after maribavir administration were not different from those in foreign clinical studies.

PMDA's view:
In view of the information obtained to date, maribavir can be expected to show antiviral activity against CMV including Japanese CMV strains.

Multiple maribavir-resistant mutations have been reported, and these mutations were confirmed to reduce the antiviral activity of maribavir by a maximum of >400-fold. Among the mutations reported, F342Y, T409M, C480F, H411Y, and H411N were also detected in the Japanese and foreign clinical studies of maribavir as well as in relapsed subjects and non-responders, especially in Studies 202 and 203. Since F342Y and C480F, among the mutations, show cross-resistance to GCV, resistant mutations induced by the clinical use of maribavir might affect the efficacy of maribavir and GCV.

Therefore, information on the sensitivity of Japanese CMV strains to maribavir and resistant mutations that affect the efficacy of maribavir should be continuously collected, including the published literature, even in the post-marketing setting. New findings should be provided to healthcare professionals immediately when they become available.

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

The applicant submitted data on absorption, distribution, metabolism, and excretion in the form of study results of oral or intravenous administration in mice, rats, and monkeys. The applicant also submitted results on plasma protein binding, distribution in blood cells, drug-metabolizing enzymes, and drug transporters obtained using biomaterials of humans and other animal species.

Plasma maribavir concentrations were measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS) (lower limit of quantitation [LLOQ] = 0.001 or 0.10 μg/mL) or HPLC (LLOQ = 0.040 μg/mL). Plasma VP44469 concentrations were measured by HPLC (LLOQ = 0.080 μg/mL). Radioactivity concentrations in biomaterials were measured by quantitative whole-body autoradiography, liquid scintillation counter detection, or HPLC with a radioactivity detector.

Unless otherwise specified, pharmacokinetic (PK) parameters are expressed using the mean or the mean ± standard deviation.

4.1 Absorption

4.1.1 Single dose (Reference CTD 4.2.2.2-2; CTD 4.2.2.2-4 and 4.2.2.2-9)

Table 13 shows PK parameters in rats and monkeys that received a single intravenous or oral dose of maribavir. The bioavailability (BA) following a single oral dose of maribavir was 98% and 66% in rats and monkeys, respectively.

Table 13. PK parameters of maribavir following a single oral dose of maribavir

Animal species (Food condition)	Route of administration	Dose (mg/kg)	N	t_{max} (h)	C_{max} (µg/mL)	AUC_{inf} (µg·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)
Rats (Unknown)	i.v.	5	3 males	-	-	1.72 ± 0.99	2.74 ± 0.90	72.6 ± 62.7	7.31 ± 5.97
	p.o.	10		0.75 [0.5, 0.75]	0.438 ± 0.077	3.30 ± 0.72	-	52.0 ± 10.1	-
Monkeys (Non-fasted)	i.v.	5	3 males	-	-	4.59 ± 0.67	11.5 ± 5.1	18.4 ± 3.0	9.36 ± 4.97
	p.o.	10		2.00 [2.00, 2.00]	1.50 ± 1.04	6.21 ± 3.59	-	32.3 ± 14.3	-

t_{max}, median (range); -, not calculated.

4.1.2 Repeated dose (CTD 4.2.3.2-2, 4.2.3.2-5, and 4.2.3.2-8)

Table 14 shows PK parameters of maribavir and the main metabolite VP44469 [see Section 4.3] in mice, rats, and monkeys that received repeated oral doses of maribavir. Both maribavir and VP44469 accumulated following repeated-dose administration in mice and rats, but neither of them accumulated in monkeys. Exposure to maribavir and VP44469 tended to be higher in females than in males in rats, exposure to VP44469 tended to be higher in males in mice, and exposure to maribavir and VP44469 did not differ between the sexes in monkeys.

Table 14. PK parameters of maribavir and VP44469 following repeated oral doses of maribavir

Animal species	Dose (mg/kg/day)	N	Measurement time point	Analyte	t_{max} (h)		C_{max} (μg/mL)		AUC[a)] (μg·h/mL)	
					Males	Females	Males	Females	Males	Females
Mice	50	4/sex/time point	Day 1	Maribavir	1.0	1.0	10.0	6.87	40.5	31.0
				VP44469	4.0	2.0	5.55	4.30	31.1	21.0
			Week 13	Maribavir	2.0	1.0	7.45	6.93	34.1	27.9
				VP44469	2.0	2.0	4.79	2.79	35.0	13.8
	150		Day 1	Maribavir	1.0	1.0	17.5	11.9	189	79.5
				VP44469	4.0	4.0	9.36	6.43	128	39.4
			Week 13	Maribavir	1.0	1.0	19.7	19.9	99.2	105
				VP44469	2.0	1.0	11.6	6.94	143	39.4
	300	4/sex/time point	Day 1	Maribavir	1.0	2.0	22.5	16.1	221	233
				VP44469	4.0	2.0	9.50	7.83	142	90.8
		3-4/sex/time point[b)]	Week 13	Maribavir	1.0	8.0	26.7	28.9	279	407
				VP44469	4.0	8.0	19.0	9.66	230	145
Rats	25	2/sex/time point	Day 1	Maribavir	1.0	1.0	1.02	2.44	6.37	12.8
				VP44469	-	1.0	-	0.0440	-	-
			Day 170	Maribavir	1.0	1.0	1.28	4.39	13.0	26.7
				VP44469	8.0	2.0	0.0480	0.244	-	3.00
	100		Day 1	Maribavir	2.0	4.0	2.81	6.56	41.9	88.6
				VP44469	2.0	4.0	0.0885	0.280	-	3.55
			Day 170	Maribavir	1.0	8.0	4.49	7.62	57.1	153
				VP44469	2.0	24	0.325	1.20	2.00	19.3
	400		Day 1	Maribavir	4.0	8.0	4.12	12.3	276	466
				VP44469	24	24	0.204	0.743	3.86	14.8
			Day 170	Maribavir	1.0	1.0	13.6	25.1	171	331
				VP44469	2.0	8.0	1.16	6.20	19.0	107
Monkeys	100[c)] (50 BID)	4/sex	Day 1	Maribavir	2 [2, 2]	2 [2, 2]	1.11 ± 0.29	2.13 ± 1.57	30.2 ± 21.4	25.0 ± 7.2
				VP44469	2 [2, 2]	2 [2, 2]	-	-	-	-
		3 males, 4 females	Week 26	Maribavir	10 [2, 10]	2 [2, 10]	2.63 ± 0.52	3.31 ± 0.77	39.5 ± 10.4	42.6 ± 4.9
				VP44469	2 [2, 10]	2 [2, 10]	0.551 [d)]	0.529 ± 0.172	6.49 [d)]	7.08 ± 1.41
	200[c)] (100 BID)	4/sex	Day 1	Maribavir	2 [2, 2]	2 [2, 10]	2.87 ± 1.02	2.02 ± 0.62	68.5 ± 23.3	45.1 ± 13.6
				VP44469	2 [2,10]	2 [2, 10]	-	-	-	-
		4 males, 3 females	Week 26	Maribavir	2 [2, 10]	2 [2, 2]	7.84 ± 2.78	6.01 ± 0.68	95.3 ± 33.6	82.4 ± 15.3
				VP44469	2 [2, 10]	2 [2, 2]	1.15 ± 0.29	0.97 ± 0.07	13.1 ± 3.7	13.0 ± 1.3
	400[c)] (200 BID)	7 males, 6 females	Day 1	Maribavir	2 [2, 10]	2 [2, 2]	5.83 ± 0.82	8.64 ± 3.26	102 ± 28	111 ± 40
				VP44469	2 [2, 10]	2 [2, 4]	0.671 ± 0.121	1.10 ± 0.36	10.9 ± 4.5	12.1 ± 2.7
		5/sex	Week 26	Maribavir	4 [2, 10]	2 [2, 10]	12.9 ± 4.8	10.2 ± 2.3	145 ± 30	106 ± 25
				VP44469	7 [2, 10]	2 [2, 10]	1.63 ± 0.41	1.70 ± 0.55	18.8 ± 4.5	17.7 ± 3.9

t_{max}, median (range); -, not calculated.

a) Mice, AUC_{last}; rats and monkeys, AUC_{inf} on Day 1 and $AUC_{0\text{-}24\ h}$ on other days. b) Plasma concentrations of maribavir and VP44469 were measured in 3 males at some measurement time points. c) Half the dose was administered from Day 1 to the day before Week 4, and the specified dose was administered thereafter during the study period. d) Individual data of 1 monkey.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.5-3; Reference CTD 4.2.3.2-6)

In albino and pigmented rats (1 rat/time point) that received a single oral dose of ^{14}C-labeled maribavir (10 mg/kg), the tissue distribution[13)] of radioactivity up to 168 hours post-dose (albino rats) or up to 504 hours post-dose (pigmented rats) was investigated. In both strains of rats, radioactivity was distributed in tissues except for the artery wall, bile, cerebellum, cerebrum, medulla oblongata, olfactory brain, lens, fat (abdomen), and spinal cord.[14)] The radioactivity concentration in the renal cortex was the highest, and high radioactivity concentrations[15)] were also observed in the adrenal gland, extraorbital lacrimal gland, kidney, renal medulla,

[13)] *In vivo* tissues investigated were as follows: adrenal gland, artery wall, bile, blood, bone, bone marrow, cerebellum, cerebrum, choroid plexus, medulla oblongata, olfactory brain, bulbourethral gland, cecum, diaphragm, epididymis, esophagus, extraorbital lacrimal gland, lens, uvea, eye, fat (abdomen), brown fat, Harderian gland, intraorbital lacrimal gland, renal cortex, renal medulla, kidney, large intestine, liver, lung, lymph node, muscle, myocardium, turbinate, pancreas, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, non-pigmented skin, pigmented skin, small intestine, spinal cord, spleen, stomach, testis, thymus, thyroid gland, bladder, urine.

[14)] In albino rats, distribution of radioactivity was also not observed in tissues including the bone, eye, and seminal vesicle.

[15)] The ^{14}C-labeled maribavir concentrations in albino and pigmented rats were >2000 ng/g.

large intestine, liver, and pancreas. In most of the tissues in which radioactivity was distributed, the radioactivity peaked by 4 hours post-dose and then decreased over time. It became undetectable by 72 hours post-dose, except for the uvea, eye, and pigmented skin in pigmented rats.

In monkeys (1 male and 1 female) that received repeated oral doses of maribavir 10, 30, or 90 mg/kg twice daily for 28 days, the maribavir concentrations in the brain and vitreous fluid on Day 28 were 3.5% to 20%[16)] and <1%, respectively, of the plasma maribavir concentration.

In rats, radioactivity was not detected in the brain tissues, except for the choroid plexus and pituitary gland, or the spinal cord, and in monkeys, the maribavir concentration in the brain was generally lower than that in plasma. The applicant therefore considered that the blood-brain-barrier penetration of maribavir is low.

The maximum radioactivity concentration in the uvea was approximately 6.6-fold higher in pigmented rats than albino rats, and the radioactivity was detectable even at 504 hours post-dose, while radioactivity concentrations were detected up to 72 hours post-dose in pigmented skin. These findings suggested that maribavir-related substances have affinity for melanin-containing tissues. However, since maribavir showed no phototoxicity up to the maximum concentration (100 μg/mL) in the *in vitro* phototoxicity study using BALB/c 3T3 mouse fibroblast cells [see Section 5.8.3], the applicant considered that accumulation of maribavir in melanin-containing tissues is unlikely to raise safety concerns.

4.2.2 Plasma protein binding (Reference CTD 4.2.2.3-4 and 4.2.2.3-6)

The protein binding rates (by equilibrium dialysis) in mouse, rat, monkey, and human plasma spiked with maribavir (0.05-20 μg/mL[17)]) were 77.8% to 86.7%, 85.9% to 90.0%, 82.2% to 85.2%, and 94.3% to 99.0%, respectively.

The protein binding rates (by equilibrium dialysis) in mouse, rat, and monkey plasma spiked with VP44469 (0.3-7.5 μg/mL) were 70.6% to 81.9%, 65.1% to 76.7%, and 75.9% to 81.0%, respectively.

4.2.3 Distribution in blood cells (Reference CTD 4.2.2.3-5; CTD 4.2.2.3-13 and 4.2.2.5-3)

The distribution in blood cells in rat and monkey blood spiked with maribavir (0.5 or 5 μmol/L) was 73.3% and 70.1%, respectively (mouse blood) and 84.3% and 77.0%, respectively (monkey blood).

The blood-to-plasma concentration ratio in human blood spiked with maribavir (0.005-10 μg/mL) was 1.18 to 1.46.

When a single oral dose of ^{14}C-labeled maribavir (10 mg/kg) was administered to albino and pigmented rats (1 rat/time point), the blood-to-plasma radioactivity concentration ratio from 0.5 to 24 hours post-dose was 1.52

[16)] In 1 female in the 90 mg/kg BID group, the maribavir concentration in the brain was 69% of that in plasma because the plasma concentration was low. However, the brain maribavir concentration in this monkey was <1/4 of that in the male in the 90 mg/kg BID group.
[17)] Up to 200 μg/mg only for human plasma.

to 2.24 (albino rats) and 1.51 to 2.08 (pigmented rats).

4.3 Metabolism

4.3.1 *In vitro* metabolism (Reference CTD 4.2.2.4-3 and 4.2.2.4-10; CTD 4.2.2.4-11 and 4.2.2.6-5)

Metabolites of ^{14}C-labeled maribavir (10 μmol/L) were investigated using rat, monkey, and human hepatic microsomes or hepatocytes. For all animal species, the results suggested that maribavir is mainly metabolized via the 3 metabolic pathways listed below. Although the metabolic profile varies among animal species, the metabolites detected in humans were also detected in rats or monkeys.

- Maribavir undergoes N-dealkylation of the isopropyl group to form VP44469, which then undergoes glucuronide conjugation to form M1.
- Maribavir undergoes glucuronide conjugation to form 3 glucuronide-conjugated isomeric metabolites (M7a, M7b, and M7c).
- The N-glycosidic bond of maribavir is cleaved to form M9 and M13, which are then metabolized via glucuronide conjugation to form M2/M3 and M8, respectively.

Investigation using human hepatic microsomes and human recombinant cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) suggested that CYP1A2 and CYP3A4 are mainly involved in the metabolism of maribavir to form the major metabolite (VP44469). The CL_{int} of CYP1A2 and CYP3A4 was 0.06 and 0.05 μL/min/pmol, respectively. When these CL_{int} values were normalized based on the expression levels of CYP1A2 and CYP3A4 in human hepatic microsomes, the percent contribution of CYP1A2 and CYP3A4 to maribavir metabolism was estimated to be 33.6% and 66.4%, respectively.

Investigation using human hepatic microsomes and human recombinant uridine 5’ diphospho glucuronosyltransferase (UGT) isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT1A10, UGT2B7, and UGT2B15) showed that UGT1A1, UGT1A3, and UGT2B7 are mainly involved in the metabolism of maribavir.

4.3.2 *In vivo* metabolism (Reference CTD 4.2.2.4-6 and 4.2.2.4-8)

In non-bile duct-cannulated male and female mice that received a single oral dose of ^{14}C-labeled maribavir, maribavir and VP44469 were mainly present in plasma, urine, and feces (48.7%-60.6%, 2.36%-4.27%, and 23.7%-26.6%, respectively[18)] [maribavir], and 34.5%-48.2%, 11.4%-24.6%, and 21.9%-33.4%, respectively[18)] [VP44469]). In bile-duct cannulated male monkeys that received a single intravenous dose of ^{14}C-labeled maribavir, M5 and M6 were mainly present in bile (34.2%[19)] [M5] and 38.6%[19)] [M6]). No metabolites were detected at >2% of the administered radioactivity in urine or feces.

[18)] For plasma, percentage relative to the total radioactivity in plasma; and for urine or feces, percentage relative to the administered radioactivity.
[19)] Percentage relative to the administered radioactivity.

4.3.3 Estimated metabolic pathway

In view of the results of the *in vitro* and *in vivo* metabolism studies described above [see Sections 4.3.1 and 4.3.2] and the human mass balance study [see Section 6.2.1.2], the metabolic pathway of maribavir in humans was estimated as shown in Figure 1.

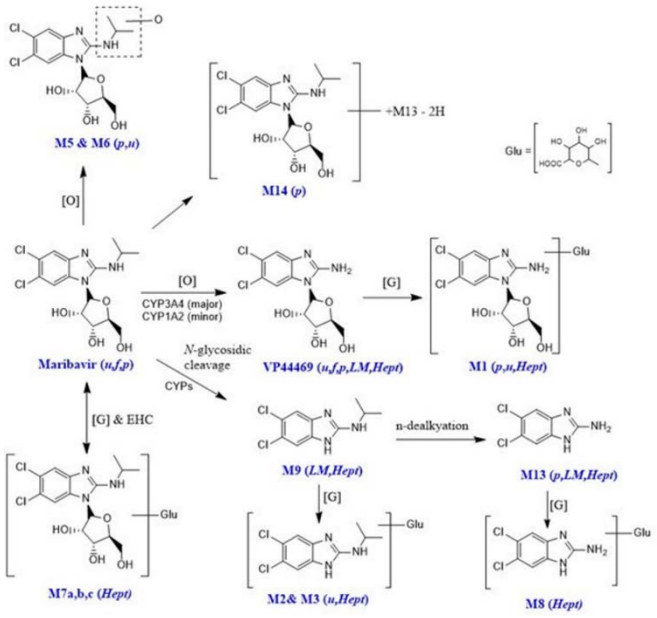

Figure 1. Putative metabolic pathway of maribavir in humans

[O], oxidation; [G], glucuronidation; EHC, enterohepatic circulation; u, urine; f, feces; p, plasma: LM, liver microsome; Hept, hepatocyte.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion (Reference CTD 4.2.2.5-1 and 4.2.2.5-2; CTD 4.2.2.5-3 and 4.2.2.5-5)

Table 15 shows the urinary, fecal, and biliary excretion of maribavir relative to the administered radioactivity in non-bile duct-cannulated male and female mice that received a single intravenous or oral dose of ^{14}C-labeled maribavir 10 mg/kg, bile duct-cannulated and non-bile duct-cannulated male rats that received a single oral dose of ^{14}C-labeled maribavir 10 mg/kg, and bile duct-cannulated and non-bile duct-cannulated male monkeys that received a single intravenous dose of ^{14}C-labeled maribavir 13 mg/kg. In bile duct-cannulated rats and monkeys, most of the ^{14}C-labeled maribavir was excreted in bile. In mice, the urinary excretion rate tended to be higher in females than in males.

Table 15. Excretion rates in mice, male rats, and male monkeys that received a single dose of ^{14}C-labeled maribavir

Animal species	Bile-duct cannulation	Route of administration	Dose (mg/kg)	N	Measurement time point (h)	Recovery relative to the administered radioactivity (%)		
						Urine	Feces	Bile
Mice	Non-cannulated	i.v.	10	6 males	0-168	23.9 ± 7.6	61.5 ± 2.8	-
				6 females		40.4 ± 8.1	44.2 ± 4.7	-
		p.o.		6 males		15.6 ± 2.8	71.4 ± 5.0	-
				6 females		33.8 ± 9.0	51.9 ± 1.7	-
Rats	Non-cannulated	p.o.	10	3 males	0-111	5.39 ± 0.45	89.2 ± 3.8	-
	Cannulated				0-168	5.34 ± 1.65	20.1 ± 3.8	80.3 ± 9.3
Monkeys	Non-cannulated	i.v.	13	3 males	0-336	14.1 ± 3.0	75.2 ± 3.8	-
	Cannulated				0-168	5.16 ± 2.88	2.36 ± 0.40	84.0 ± 4.6

-, not calculated.

4.5 Pharmacokinetic interactions

4.5.1 Inhibition of drug-metabolizing enzymes (Reference CTD 4.2.2.6-1 and 4.2.2.6-4; CTD 4.2.2.6-2, 4.2.2.6-3, and 4.2.2.6-5)

The direct and time-dependent inhibitory effects of maribavir (0.1-100 μmol/L) and the direct inhibitory effect of VP44469 (0.1-30 μmol/L) on CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were investigated using human hepatic microsomes.[20)] The results are as follows:

- While maribavir directly inhibited CYP3A4 (substrate, nifedipine), CYP1A2, CYP2C9, and CYP2C19, with a 50% inhibitory concentration (IC_{50}) of 50, 40, 18, and 35 μmol/L, respectively, maribavir did not directly inhibit CYP3A4 (substrates, midazolam and testosterone) or the other isoforms (IC_{50} >100 μmol/L).
- Maribavir time-dependently inhibited CYP3A4 (substrates, midazolam and testosterone). The K_i (concentration required for half-maximal inactivation rate) and K_{inact}[21)] (maximal inactivation rate constant) for the metabolic activity of CYP3A4 were 41.2 μmol/L and 0.0117 min^{-1}, respectively (midazolam) and 167 μmol/L and 0.0357 min^{-1}, respectively (testosterone).
- VP44469 directly inhibited CYP3A4 (substrate, testosterone) (IC_{50}, approximately 30 μmol/L), but did not directly inhibit CYP3A4 (substrates, midazolam and nifedipine) or the other isoforms (IC_{50} >30 μmol/L).

The inhibitory effect of maribavir (0.1-500 μmol/L) on UGT isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was investigated using human hepatic microsomes.[22)] Maribavir inhibited UGT1A1, UGT1A3, UGT1A9, and UGT2B7, with an IC_{50} of 32.3, 184, 123, and 153 μmol/L, respectively.

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20) Compounds used as substrates of the isoforms in the investigation of the direct inhibitory effect of maribavir and VP44469: CYP1A2, phenacetin; CYP2A6, coumarin; CYP2B6, bupropion; CYP2C8, paclitaxel; CYP2C9, tolbutamide; CYP2C19, (S)-mephenytoin; CYP2D6, dextromethorphan; CYP2E1, chlorzoxazone; CYP3A4, midazolam, nifedipine, and testosterone.
Compounds used as substrates of the isoforms in the investigation of the time-dependent inhibitory effect of maribavir: CYP1A2, phenacetin; CYP2B6, bupropion; CYP2C8, amodiaquine; CYP2C9, diclofenac; CYP2C19, (S)-mephenytoin; CYP2D6, bufuralol; CYP3A4, midazolam and testosterone.

21) K_i and k_{inact} for the metabolic activity of CYP3A4 were investigated in the maribavir concentration range of 0 to 250 μmol/L.

22) Compounds used as substrates of the isoforms: UGT1A1, β-estradiol; UGT1A3, chenodeoxycholic acid; UGT1A4, trifluperazine; UGT1A6, 4-hydroxyindole; UGT1A9, propofol; UGT2B7, zidovudine.

4.5.2 Induction of drug-metabolizing enzymes (CTD 4.2.2.6-7; Reference CTD 4.2.2.6-11)

The inductive effect of maribavir (0.5-100 μmol/L) on CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated based on the expression level of mRNA using human hepatocytes. The results suggested that maribavir induces CYP1A2 and CYP3A4, but that it does not induce CYP2B6.

4.5.3 Assessment of maribavir as a substrate for drug transporters (CTD 4.2.2.6-8 and 4.2.2.6-9)

Investigation using Madin-Darby canine kidney (MDCK) cells engineered to express P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) and non-expressing MDCK cells[23)] suggested that maribavir is a substrate of P-gp and BCRP.

Using HEK293 cells engineered to express organic anion transporting polypeptide (OATP)1B1, OATP1B3, or organic cation transporter (OCT)1, and non-expressing HEK293 cells, the uptake rate of each transporter substrate was investigated.[24)] The results suggested that maribavir is unlikely to be a substrate of OATP1B1 and OATP1B3, and that it is a substrate of OCT1.

Investigation using membrane vesicles engineered to express the human bile salt export pump (BSEP) suggested that maribavir is unlikely to be a substrate of BSEP.

4.5.4 Inhibition of drug transporters (CTD 4.2.2.6-8, 4.2.2.6-9, and 4.2.2.6-10)

Using human epithelial colorectal adenocarcinoma (Caco-2) cells, clone of Caco-2 cell line (C2BBe1) cells, HEK293 cells engineered to express human OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, OCT1, OCT2, multidrug and toxin extrusion (MATE)1, or MATE2K, and membrane vesicles engineered to express BSEP, the inhibitory effect of maribavir and VP44469 on transporters was investigated.[25)] Table 16 shows the results.

Table 16. Inhibition of transporters by maribavir and VP44469

Transporter	Analyte	Concentrations investigated (μmol/L)	IC_{50} (μmol/L)	Transporter	Analyte	Concentrations investigated (μmol/L)	IC_{50} (μmol/L)
OAT1	Maribavir	36	>36	P-gp	Maribavir	0.274-200	33.8
	VP44469	15.5	>15.5	BCRP	Maribavir	0.9-220	7.05
OAT3	Maribavir	1.4-360	33.3	OATP1B1	Maribavir	9-2,200	45.5
	VP44469	15.5	>15.5	OATP1B3	Maribavir	9-2,200	49.4
OCT2	Maribavir	36	>36	OCT1	Maribavir	9-2,200	344
	VP44469	15.5	>15.5	BSEP	Maribavir	1.48-359	46.5
MATE1	Maribavir	1.4-360	20.4				
	VP44469	15.5	>15.5				
MATE2K	Maribavir	36	>36				
	VP44469	15.5	>15.5				

[23)] The ratio of apparent permeability of the basolateral-to-apical direction to that of apical-to-basolateral direction of maribavir (efflux ratio) was investigated. Compounds used as inhibitors of the transporters: P-gp, cyclosporine A and ketoconazole; BCRP, Ko143.

[24)] Additional investigation using inhibitors was specified to be conducted if the ratio of the uptake rate in transporter-expressing cells to that in non-expressing cells exceeded 2.

[25)] For VP44469, the inhibitory effect on OAT1, OAT3, OCT2, MATE1, and MATE2K was investigated. Substrates of the transporters: P-gp, digoxin; BCRP, cladribine; OATP1B1 and OATP1B3, atorvastatin; OAT1, para-aminohippurate; OAT3, furosemide; OCT1 and OCT2, 1-methyl-4-phenylpyridinium iodide; MATE1 and MATE2K, metformin; BSEP, [^{3}H]taurocholic acid.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the non-clinical PK properties of maribavir were confirmed. Since maribavir is mainly metabolized by CYP3A4, and its inhibition and induction of drug-metabolizing enzymes and drug transporters are suggested, the clinical use of maribavir may induce significant drug interactions. Therefore, this possibility is further discussed in Section 6.R.1, also taking the results of clinical drug interaction studies [see Section 6.2.4] into account.

5. Toxicology and Outline of the Review Conducted by PMDA

Toxicity studies of maribavir include single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, studies in juvenile animals, local tolerance studies, and other toxicity studies (an immunotoxicity study, a phototoxicity study, toxicity evaluation of impurities, and toxicity evaluation of metabolites). Unless otherwise specified, citrate buffer solution was used as the vehicle.

5.1 Single-dose toxicity

Single oral and intravenous dose toxicity studies in mice and rats were conducted (Table 17). The approximate lethal dose of maribavir following oral administration was considered to be 500 mg/kg in mice and 1,000 mg/kg in rats. The main acute symptoms were decreased activity, collapse, convulsions, abnormal vocalization, gasping respiration, and ataxic gait in mice, and salivation, decreased activity, collapse, labored respiration, tremors, and loose stools in rats. The approximate lethal dose of maribavir following intravenous administration was considered to be 37.5 mg/kg in mice and 87.5 mg/kg in rats. The main acute symptoms were convulsions, ataxic gait, gasping/labored respiration, collapse, side-lying position, decreased activity, and ptosis in mice, and convulsions, gasping respiration, shallow/labored respiration, collapse, and decreased activity in rats. Acute toxicity following oral administration in cynomolgus monkeys was evaluated in the repeated oral dose toxicity study (CTD 4.2.3.2-8). No deaths or acute symptoms were observed at the initial dose of up to 400 mg/kg/day, and the approximate lethal dose of maribavir was considered to be >400 mg/kg/day.

Table 17. Summary of single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached data CTD
Male and female mice (CD-1)	p.o. (gavage)	250, 500, 1000	500: Death, 2/5 animals (males), 3/5 animals[a)] (females) 1000: Death, 5/5 animals[a)] (males and females) Decreased activity, collapse, convulsions, abnormal vocalization, gasping respiration, ataxic gait	500	4.2.3.1-1
Male and female mice (CD-1)	i.v.	25 (only males), 37.5, 43.75, 50, 62.5 (only females)	37.5: Death, 3/5 animals (males) 43.75: Death, 2/5 animals (males), 1/5 animals (females) 50: Death, 5/5 animals (males), 1/5 animals (females) 62.5: Death, 5/5 animals (females) Clonic convulsion, ataxic gait, gasping/labored respiration, collapse, side-lying position, decreased activity, ptosis	Males: 37.5 Females: 43.75	4.2.3.1-2
Male and female rats (SD)	p.o. (gavage)	1,000, 1,500, 2,000	1000: Death, 1/5 animals (males) ≥1500: Death, 5/5 animals (males and females) Salivation, decreased activity, soiled fur in the anogenital area, collapse, labored respiration, tremor, white/clear and viscous substance/yellow massive content in the stomach/intestine, spongy changes in the lung	Males: 1,000 Females: 1,500	4.2.3.1-3
Male and female rats (SD)	i.v.	Males: 75, 100, 150, 175, 200 Females: 50, 75, 87.5, 100	87.5: Death, 1/5 animals (females) 100: Death, 2/5 animals (males), 5/5 animals (females) ≥150: Death, 5/5 animals (males) Decreased activity, shallow/labored respiration, tonic/clonic convulsion, collapse, gasping respiration	Males: 100 Females: 87.5	4.2.3.1-4

a) Death of 1 female in the 500 mg/kg group and 1 female in the 1,000 mg/kg group were considered due to an error in dosing.

5.2 Repeated-dose toxicity

A 30-day repeated oral dose toxicity study in rats, a 26-week repeated oral dose toxicity study in rats, and a 13-week repeated oral dose toxicity study in mice were conducted (Table 18). The main toxicity findings of maribavir were death associated with worsening of clinical signs, mucosal hyperplasia in the small and large intestine/intestinal distention, and increased hematopoiesis related to decreases in red blood cell parameters in rats, and mucosal erosion/ulcers in the stomach/small and large intestine, mucosal epithelial hyperplasia in the small and large intestine, and increased hematopoiesis in mice. Other toxicity findings included increased bilirubin in rats and increased blood ALP and bilirubin in mice. Laboratory abnormalities in hematological parameters, renal function parameters, lipids, proteins, and electrolytes were observed in rats. However, these findings were mild, and no clinically significant abnormalities related to these findings were observed in clinical studies. Therefore, safety concerns were considered unlikely to arise in humans. Increased adrenal gland weight and decreased thymic weight in rats were considered to be stress-related secondary changes. Cytoplasmic changes in liver cells accompanied by increased liver weight in rats were considered to be related to the induction of drug-metabolizing enzymes by maribavir [see Section 4.5.2].

Unbound maribavir exposure ($AUC_{0\text{-}24h}$) at the no observed adverse effect level (NOAEL, 25 mg/kg/day for both males and females) following repeated oral dose administration of maribavir for 26 weeks in rats was 1.54 μg·h/mL in males and 3.18 μg·h/mL in females. These exposures were approximately 0.27 times (in

males) and approximately 0.56 times (in females) the unbound maribavir exposure[26)] following oral dose administration of maribavir in humans at the human dose ($AUC_{0\text{-}24h}$, 5.68 μg·h/mL; hereinafter referred to as "human exposure").

Table 18. Summary of repeated-dose toxicity studies in rodents

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Male and female rats (SD)	p.o. (gavage)	30 days (once daily) + 17-day recovery period	0, 100, 200, 400	≥100: Salivation, changes in stool properties, increased reticulocyte count, cecal distention, duodenal villus hyperplasia, mucosal hyperplasia in the cecum/colon, decreased colonic mucosal cell count (males and females), increased total white blood cell count/neutrophil count/lymphocyte count/monocyte count, increased adrenal gland/spleen weights (females) ≥200: Soiled anogenital area, increased total white blood cell count/lymphocyte count/monocyte count, colonic distention (males), increased adrenal gland weight, increased blood total bilirubin, increased liver weight (females) 400: Increased neutrophil count, colonic distention, bronchial epithelial degeneration (males), soiled anogenital area, red blood cell growth in the spleen, red blood cell growth in the liver (females) 200: Bronchial epithelial degeneration (females) Reversibility: Reversible	<100	4.2.3.2-4
Male and female rats (Wistar)	p.o. (gavage)	26 weeks (once daily) + 4-week recovery period	0, 25, 100, 400	[Death or early necropsy] 400: Death, 1/24 animals (males), 4/24 animals (females) Gasping respiration, decreased activity, loose stool, salivation, soiled fur around the anogenital area, labored respiration, decreased body surface temperature, rough fur, mucosal hyperplasia in the digestive tract, interstitial pneumonia, congestion in the duodenum/jejunum, mesenteric lymph node/thymic lymphocyte necrosis, lymphoid tissue atrophy in the spleen [Surviving animals] ≥25: Salivation, brown pigment deposition in the tubular epithelium of the renal cortex (males and females), decreased red blood cell count, increased mean corpuscular volume, decreased blood total protein/ALP, mucosal hyperplasia in the cecum (males), mucosal infiltration of lymphocytes in the cecum/colon/rectum (females) ≥100: Loose stool/mucous stool, soiled anogenital area, decreased body weight/weight gain, decreased urinary potassium/sodium, increased neutrophil count, increased mean corpuscular hemoglobin concentration, decreased blood creatinine, mucosal hyperplasia in the colon (males and females), increased diuresis, decreased urinary creatinine, decreased eosinophil count, increased blood albumin/globulin (A/G) ratio, decreased blood globulin/calcium/triglycerides, changes in the cytoplasm of centrilobular hepatocytes in the liver (males), increased mean corpuscular volume, decreased red blood cell count/hematocrit, increased blood phosphorus, decreased blood total protein/albumin/urea nitrogen, mucosal hyperplasia	25	4.2.3.2-5

[26)] Calculated taking into account the steady-state exposure to maribavir following twice-daily administration of maribavir 400 mg in organ transplant recipients (including HSCT recipients) infected with CMV ($AUC_{0\text{-}24}$ was estimated to be 284 h·μg/mL [2×$AUC_{\tau,ss}$] based on $AUC_{\tau,ss}$ [142 h·μg/mL) and the plasma protein-unbound fraction of maribavir in humans (2%; CTD 4.2.2.3-6).

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
				in the cecum (females) Reversibility: Reversible		
Male and female mice (CD-1)	p.o. (gavage)	13 weeks (once daily) + 12-week recovery period	0, 50, 150, 300, 500	[Death or early necropsy] 300: 4/64 animals (males), 2/64 animals (females) 500: 15/64 animals (males), 16/64 animals (females) Decreased stool, irregular respiration, respiratory sound, labored respiration, clear oral secretion, coarse fur, head tremor, decreased activity [Surviving animals] ≥150: Coarse fur, clear oral secretion, increased mean corpuscular volume/mean corpuscular hemoglobin concentration (males) ≥300: Hunchback position, decreased stool, irregular respiration, increased reticulocyte count, decreased lymphocyte count, increased liver weight (males and females), incomplete eyelid opening, increased blood bilirubin/ALP, hypertrophy of centrilobular hepatocytes in the liver (males), coarse fur, clear oral secretion, increased mean corpuscular volume/neutrophil count, increased spleen weight (females) 500: Mucosal hyperplasia in the cecum, inflammation in the cecum, erosion/ulcer in the colon (males and females), erosion/ulcer in the anterior stomach/cecum, mucosal hyperplasia in the colon (males), incomplete eyelid opening, increased mean corpuscular hemoglobin concentration/total bilirubin, hypertrophy of centrilobular hepatocytes in the liver, erosion/ulcer in the glandular stomach, mucosal hyperplasia in the duodenum, edema in the cecum/colon, inflammation in the colon 300: Mucosal hyperplasia in the anterior stomach (females) Reversibility: Reversible	150	4.2.3.2-2

Thirty-day, 26-week, and 52-week repeated oral dose toxicity studies in cynomolgus monkeys were conducted (Table 19). The main toxicity findings were death associated with worsening of clinical signs, decreased food consumption/body weight, dehydration, diarrhea, loose stools, debilitation, and mucosal epithelial necrosis/hyperplasia in the large intestine. Other toxicity findings included changes related to decreases in red blood cell parameters, increased blood triglycerides, decreased diuresis, and laboratory abnormalities in urinary electrolytes. These findings were considered to be secondary changes to decreased body weight and food consumption of the animals due to loose stools/diarrhea/gastrointestinal disorder and worsening of clinical signs. In addition to the above, increased liver weight was observed as an abnormal finding, but it was considered to be of low toxicological significance because there were no related abnormal findings. When maribavir was administered as repeated oral doses twice daily for 52 weeks, toxicity occurred even at a low dose, and the NOAEL could therefore not be determined.

Table 19. Summary of repeated-dose toxicity studies in non-rodents

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Male and female cynomolgus monkeys	p.o. (gavage)	30 days (twice daily) + 2-week recovery period	0, 20, 60, 180	No abnormality	180	4.2.3.2-7
Male and female cynomolgus monkeys	p.o. (gavage)	26 weeks (twice daily) + 4-week recovery period	0, 50/100,[a)] 100/200,[a)] 200/400[a)]	≥50/100: Mucosal hyperplasia in the cecum/colon (males and females), loose stool/liquid stool, dehydration, decreased urinary sodium (females) 100/200: Debilitation (females) ≥100/200: Mucosal hyperplasia in the rectum (males and females), loose stool/liquid stool (males), decreased activity, emaciation, decreased red blood cell count/hemoglobin/hematocrit, decreased urinary sodium, increased liver weight (females) 200/400: Debilitation, dehydration, decreased activity, emaciation, decreased red blood cell count/hemoglobin/hematocrit, increased liver weight (males), increased reticulocyte count (females) Reversibility: Reversible	<50/100	4.2.3.2-8
Male and female cynomolgus monkeys	p.o. (gavage)	52 weeks (twice daily) + 4- or 8-week recovery period	0, 100, 200, 400/300[b)]	[Death or early necropsy] 200: 1/4 animals (males) 400/300: 2/6 animals (males) Diarrhea, loose stool, decreased activity, anorexia, hunchback position, dehydration, rectal prolapse, debilitation, decreased red blood cell count, decreased hematocrit, mucosal epithelial hyperplasia in the cecum/colon, crypt abscess in the cecum/colon, acute inflammation in the rectum, lymphoid tissue atrophy in the spleen/thymus/lymph nodes, renal tubular dilatation, structural dilation/cists in the cecum/rectal gland, mucosal epithelial necrosis in the rectum, intra-alveolar fibrin in the lung, etc. [Surviving animals] ≥100: Diarrhea, loose stool, mucosal hyperplasia in the cecum/colon (males and females), decreased body weight, increased neutrophil count, mucosal hyperplasia in the rectum (males) ≥200: Decreased activity, hunchback position, increased reticulocyte count, decreased hematocrit, increased blood triglycerides (males and females), mucosal hyperplasia in the rectum (females) 400/300: Decreased blood ALP (males and females), dehydration (males), decreased red blood cell count/lymphocyte count (females) Reversibility: Reversible	<100	4.2.3.2-9

a) From Week 4, the dose was doubled to 100, 200, or 400 mg/kg/day. b) At the end of Week 10, treatment was interrupted for 4 weeks. From Week 14, the dose was reduced to 300 mg/kg/day. At Week 36, treatment was discontinued, followed by necropsy.

5.3 Genotoxicity

Genotoxicity studies consisted of a bacterial reverse mutation assay (Ames test), a gene mutation assay in cultured mammalian cells, and a rat micronucleus assay (Table 20). In 3 repetitions of the gene mutation test using cultured mammalian cells, a slight increase in the frequency of mutations was observed. An increase in small colonies was primarily observed, indicating clastogenic potential. However, the results of the Ames test and the rat micronucleus assay were negative. Therefore, maribavir is considered unlikely to be genotoxic.

Table 20. Summary of genotoxicity studies

Study		Test system	Metabolic activation (duration of treatment)	Concentration or dose	Result	Attached data CTD
In vitro	Ames test	*Salmonella typhimurium*: TA98, TA100, TA102, T1535, TA1537	S9−/+	0,[a] 6.5, 20.5, 65, 205.5, 650 μg/plate	Negative	4.2.3.3.1-1
	Gene mutation assay	Mouse lymphoma cells L5178Y/*tk*$^{+/-}$	S9− (4 hours, soft agar plate assay)	0,[a] 10, 20, 30, 50, 75, 100, 200 μg/mL	Indeterminate[b]	4.2.3.3.1-2
			S9+ (4 hours, soft agar plate assay)	0,[a] 10, 20, 30, 50, 75, 100, 200 μg/mL	Negative	
			S9− (3 hours, micro-titer assay)	Test 1: 0,[a] 50, 75, 100, 200 μg/mL	Positive	4.2.3.3.1-3
				Test 2: 0,[a] 50, 100, 125, 150, 175, 200 μg/mL	Positive	
			S9− (24 hours, micro-titer assay)	Test 1: 0,[a] 5, 10, 15, 20, 25, 50, 75 μg/mL	Positive	4.2.3.3.1-4
				Test 2: 0,[a] 5, 10, 15, 20, 25, 50 μg/mL	Positive	
			S9+ (3 hours, micro-titer assay)	Test 1: 0,[a] 20, 25, 50, 75, 100, 150 μg/mL	Positive	
				Test 2: 0,[a] 5, 10, 25, 52, 75 μg/mL	Negative	
In vivo	Rat micronucleus assay	Male and female rat (SD) bone marrow		0, 400, 800, 1200 mg/kg/day (p.o., single dose)	Negative	4.2.3.3.2-1

a) Dimethyl sulfoxide (DMSO). b) Slight increases (approximately 1.5-fold and 2.2-fold) in the frequency of mutations were observed at 100 and 200 μg/mL, but they did not meet the positive criterion. Therefore, the result was indeterminate, and an additional test was planned.

5.4 Carcinogenicity

A 2-year oral dose carcinogenicity study in mice was conducted (Table 21). As neoplastic lesions related to maribavir administration, the incidence of hemangioma, angiosarcoma, and concurrent hemangioma/angiosarcoma increased in males in the maribavir groups. Bronchioloalveolar adenoma, adenocarcinoma, and adenoma/adenocarcinoma were observed in males in the maribavir groups, and the incidence of uterine adenoma, adenocarcinoma, and adenoma/adenocarcinoma tended to be high in females in the maribavir groups, although their incidence was within the historical laboratory data. Therefore, these findings were considered unlikely to be related to maribavir administration. As non-neoplastic lesions, hypertrophy of centrilobular hepatocytes in the liver and increased extramedullary hematopoiesis in the spleen were observed. The non-carcinogenic dose was considered to be 75 mg/kg/day in males and 150 mg/kg/day in females. Unbound maribavir exposure ($AUC_{0\text{-}24h}$) at 75 mg/kg/day was 13.77 μg·h/mL in males and 9.72 μg·h/mL in females, and the exposures were approximately 2.4 times and approximately 1.7 times the human exposure, respectively.

Table 21. Summary of the carcinogenicity study in mice

Test system	Route of administration	Administration period	Main lesions	Sex	Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached data CTD
					0	0	25	75[b)]	150[b)]		
				N	60/sex	60/sex	60/sex	M: 79 F: 81	M: 77 F: 75		
Male and female mice (CD-1)	p.o. (gavage)	2 years (once daily)	Neoplastic lesions							M: 75 F: 150	4.2.3.4.1-1
			Whole body[a)]/ hemangioma	M	1	0	0	0	4		
				F	2	1	1	3	0		
			Whole body[a)]/ angiosarcoma	M	3	1	4	5	10		
				F	1	7	2	1	5		
			Whole body[a)]/ hemangioma/ sarcoma	M	4	1	4	5	14*		
				F	3	8	3	4	5		
			Liver/ angiosarcoma	M	3	1	0	3	7		
				F	0	2	0	0	1		
			Spleen/ angiosarcoma	M	0	0	2	1	2		
				F	0	1	0	0	0		
			Skeletal muscle/ angiosarcoma	M	0	0	0	2	1		
				F	0	0	0	0	0		
			Uterus/adenoma	M	-	-	-	-	-		
				F	0	0	0	1	0		
			Uterus/ adenocarcinoma	M	-	-	-	-	-		
				F	0	0	1	1	3		
			Uterus/adenoma and adenocarcinoma	M	-	-	-	-	-		
				F	0	0	1	2	3		
			Lung/ bronchioloalveolar adenoma	M	12	13	11	20	12		
				F	5	8	5	13	3		
			Lung/ bronchioloalveolar adenocarcinoma	M	2	3	2	9	9		
				F	4	3	3	5	2		
			Lung/ bronchioloalveolar adenoma and adenocarcinoma	M	13	16	13	26	19		
				F	9	11	8	17	5		
			Testis/interstitial cell tumor	M	2	4	6	4	5		
				F	-	-	-	-	-		
			Other findings								
			Mortality (%)	M	38	52	43	54	56		
				F	53	48	58	54	69		
			≥75: Hypertrophy of centrilobular hepatocytes in the liver, increased extramedullary hematopoiesis in the spleen (males) 150: Increased extramedullary hematopoiesis in the spleen (females)								

M, males; F, females; *, changes related to maribavir administration; -, not applicable.
a) Total number of animals with lesions in organs/tissues of the whole body. b) Since more animals than expected died in the main study groups of 75 and 150 mg/kg/day, surviving animals in the toxicokinetic (TK) study groups of the same doses were used for carcinogenicity evaluation from Week 54.

A 2-year oral dose carcinogenicity study in rats was conducted (Table 22). Administration of maribavir did not increase the incidence of neoplastic or non-neoplastic lesions. The incidence of interstitial cell tumor in the testis in males and hepatocellular adenoma in the liver in females in the maribavir groups exceeded the historical laboratory data. However, the difference was not statistically significant, and an increase in preneoplastic lesions related to hepatocellular adenoma in the liver was not observed. These findings were therefore considered unlikely to be related to maribavir administration. The non-carcinogenic dose was considered to be 100 mg/kg/day in both males and females. Unbound maribavir exposure ($AUC_{0\text{-}24h}$) at the non-carcinogenic dose was 5.96 μg·h/mL in males and 11.02 μg·h/mL in females, and the exposures were approximately 1.1 times and approximately 1.9 times the human exposure, respectively.

Table 22. Summary of the carcinogenicity study in rats

Test system	Route of administration	Administration period	Main lesions	Sex	Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached data CTD
					0	0	10	30	100		
				N	60/sex	60/sex	60/sex	60/sex	60/sex		
Male and female rats (Wistar)	p.o. (gavage)	2 years (once daily)	Neoplastic lesions							100	4.2.3.4.1-2
			Whole body[a)]/ hemangioma	M	2	4	4	3	5		
				F	1	1	2	1	1		
			Whole body[a)]/ angiosarcoma	M	0	1	0	0	0		
				F	0	0	1	0	2		
			Testis/interstitial cell tumor	M	0	0	3	3	4		
				F	-	-	-	-	-		
			Liver/hepatocellular adenoma	M	1	0	1	2	2		
				F	1	0	1	3	4		
			Other findings								
			Mortality (%)	M	35	26.7	36.7	31.7	43.3		
				F	46.7	46.7	43.3	40	41.7		

M, males; F, females; -, not applicable.

a) Total number of animals with lesions in organs/tissues of the whole body.

5.5 Reproductive and developmental toxicity

A study of fertility and embryo-fetal development in rats was conducted (Table 23). Administration of maribavir decreased the linear velocity of sperm in males and increased pre- and post-implantation loss in females, but no effects on fertility were observed in male or female parental animals. The number of viable fetuses decreased with increasing pre- and post-implantation loss; the NOAEL of maribavir for early embryonic and fetal development can therefore not be determined. An embryo-fetal development toxicity study was conducted in rabbits. No effects on embryo-fetal development were observed with maribavir administration. Unbound maribavir exposure ($AUC_{0\text{-}24h}$) at the NOAEL of maribavir for embryo-fetal development (100 mg/kg/day) was 11.78 μg·h/mL, and it was approximately 2.1 times the human exposure. A study of pre- and postnatal development, including maternal function, in rats was conducted. Total litter loss, decreased offspring viability, and growth retardation associated with development of general toxicity in maternal animals were observed at ≥150 mg/kg/day. Estimated unbound maribavir exposure ($AUC_{0\text{-}24h}$) at the NOAEL for maternal animals and offspring (50 mg/kg/day) was 7.54 μg·h/mL, and it was approximately 1.3 times the human exposure. In view of the above study results, the applicant explained that precautions would be provided in the package insert to ensure that maribavir should preferably not be administered to pregnant or possibly pregnant women and that breastfeeding women who receive maribavir should preferably stop breastfeeding.

Table 23. Summary of reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Fertility, embryo-fetal development	Male and female rats (Wistar)	p.o. (gavage)	Males: 29 days before mating to the day of planned necropsy (10 weeks) Females: 15 days before mating to Gestation Day 17 (once daily)	0, 100, 200, 400	Parental animals ≥100: Salivation, decreased weight gain/food consumption (males and females) 400: Decreased testis weight (males) Fertility/early embryonic development ≥100: Decreased linear velocity of sperm, increased early resorptions/post-implantation loss Embryo-fetal development Decreased number of viable fetuses	General toxicity in parental animals: 100 Early embryonic development: <100 Embryo-fetal development: <100	4.2.3.5.1-2
Embryo-fetal development	Female rabbits (NZW)	p.o. (gavage)	Gestation Days 8 to 20 (once daily)	0, 25, 50, 100	Maternal animals: No effects Embryo-fetal development No effects	Maternal animals: 100 Embryo-fetal development: 100	4.2.3.5.2-3
Pre- and postnatal development, including maternal function	Female rats (Wistar)	p.o. (gavage)	Gestation Day 7 to 21 after birth (once daily)	0, 50, 150, 400	Maternal animals: [Death] 150: (1/24 animals), 400: (2/24 animals) [Surviving animals] ≥150: Salivation, soiled fur, wheezing, licking chops, decreased weight gain/food consumption, total fetal loss, total litter loss 400: Loose stool F_1 offspring ≥150: Decreased viability, delayed pinna unfolding 400: Suppressed weight gain, delayed eyelid opening/preputial separation F_2 offspring None	Maternal animals (general toxicity/fertility): 50 F_1 offspring (general toxicity/fertility): 50 F_2 offspring (general toxicity): 400	4.2.3.5.3-1

5.6 Studies in juvenile animals

A repeated oral dose toxicity study in juvenile rats was conducted (Table 24). No new toxicity findings specific to juvenile animals that had not been observed in mature animals were observed. The NOAEL in the study using fixed doses was considered to be 100 mg/kg/day, and the NOAEL in the study using dose escalation was determined to be 25 to 300 mg/kg/day in males and 25 to 225 mg/kg/day in females.

Table 24. Summary of repeated-dose toxicity studies in juvenile animals

Test system	Route of administration	Administration period	Dose (mg/kg)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Male and female juvenile rats (SD)	p.o. (gavage)	7 to 34 days after birth (once daily) + 4-week recovery period	0,[a] 25, 50, 100	No effects	100	4.2.3.5.4-2
Male and female juvenile rats (SD)	p.o. (gavage)	7 to 34 days after birth (once daily) + 4-week recovery period	0[a] (males and females), 17-200,[b] 25-300,[b] (males), 17-150,[b] 25-225[b] (females)	≥17-200 (males), 25-225 (females): Increased reticulocyte count, increased mean corpuscular volume 25-300 (males), 25-225 (females): Increased hemoglobin distribution width Reversibility: Reversible	Males: 25-300 Females: 25-225	4.2.3.5.4-3

a) 25 mM citric acid (pH 2). b) 7 to 14 days after birth, dosing of 17 and 25 mg/kg/day; 15 to 30 days after birth, dose escalation (males, 20-180 or 30-270 mg/kg/day; females, 20-150 or 30-225 mg/kg/day); 31 to 34 days after birth, 200 or 300 mg/kg/day (males) and 150 or 225 mg/kg/day (females).

5.7 Local tolerance

Skin irritation studies in rats and rabbits and an eye mucous membrane irritation study in rabbits were conducted (Table 25). Maribavir was determined to be non-irritant to rat and rabbit skin and to be corrosive to rabbit eye mucosa.

Table 25. Summary of local tolerance studies

Test system	Site of local application	Test method	Main findings	Attached data CTD
Male and female rats (Wistar)	Skin	Maribavir 2000 mg/kg was applied as a single dose with semi-occlusion to the dorsal skin for 24 hours.	Scattered small scabs (Classified as a non-skin irritant)	4.2.3.6-1
Male rabbits (NZW)	Skin	Maribavir 500 mg moistened with 0.5 mL of distilled water was applied as a single dose with semi-occlusion to the dorsal skin for 4 hours.	No irritation (Classified as a non-skin irritant)	4.2.3.6-3
Male rabbits (NZW)	Eye mucosa	Maribavir 10 mg or 57 mg (0.1 mL) was administered as a single dose into the conjunctival sac of the right eye.	10 mg: Redness/edema/secretion in the nictitating membrane (moderate) Reversibility: Reversible (Classified as an eye irritant) 57 mg: Diffuse opacity/angiogenesis in the cornea (moderate), inflammation in the iris, redness/edema/secretion in the conjunctiva (moderate), petechia/pale area in the conjunctiva, hair loss around the eye (moderate) Reversibility: After the end of treatment Diffuse opacity and angiogenesis in the cornea (Classified as an eye corrosive)	4.2.3.6-4

5.8 Other studies

5.8.1 Skin sensitization

A skin sensitization study in guinea pigs was conducted (Table 26). Maribavir showed no skin sensitization.

Table 26. Summary of the skin sensitization study

Study	Test system	Test method	Main findings	Attached data CTD
Maximization method	Guinea pigs (Hartley)	1% Maribavir (0.1 mL) was intradermally administered into the shoulder region and a patch to which maribavir 50% was applied was applied to the region for sensitization. A patch to which maribavir 25% or 50% was applied was used for challenge.	No skin sensitization	4.2.3.6-2

5.8.2 Immunotoxicity

A study on T-cell-dependent antibody production in rats was conducted. No effects of maribavir on antibody production was observed (Table 27).

Table 27. Summary of the immunotoxicity study

Study	Test system	Test method	Main findings	Attached data CTD
T-cell-dependent antibody production	Male and female rats (SD)	Maribavir 0, 10, 30, and 100 mg/kg/day were administered as repeated oral doses for 7 days. Sheep red blood cells (SRBCs) were intravenously administered 4 days before necropsy, and the number of anti-SRBC antibody producing cells among splenocytes was measured.	None	4.2.3.7.2-1 (Reference)

5.8.3 Phototoxicity

Since maribavir has an ultraviolet absorption maximum at 309 or 296 nm and absorbs ultraviolet-B (UVB) radiation, an *in vitro* phototoxicity study was conducted. Maribavir was not phototoxic (Table 28).

Table 28. Summary of the phototoxicity study

Study	Test system	Test method	Main findings	Attached data CTD
Phototoxicity	Mouse fibroblast cells (Balb/c 3T3)	Maribavir 0,[a] 1.78, 3.16, 5.62, 10.0, 17.8, 31.6, 56.2, 100 μg/mL UVA (5 J/cm^2) and UVB (22 mJ/cm^2) were irradiated.	PIF: -[b] MPE: 0.053, 0.003 No phototoxicity	4.2.3.7.7-1

a) DMSO. b) Not calculated because maribavir was not cytotoxic.

5.8.4 Toxicity evaluation of metabolites

VP44469 was identified as a metabolite detected at >10% of exposure to all substances related to maribavir administration in humans [see Section 6.2.1.2]. Since VP44469 was detected at >50% of the human exposure level in studies including the 26-week oral dose toxicity study in rats (CTD 4.2.3.2-5), 52-week oral dose toxicity study in cynomolgus monkeys (CTD 4.2.3.2-9), carcinogenicity study in mice (CTD 4.2.3.4.1-1), and fertility and embryo-fetal development toxicity study in rats (CTD 4.2.3.5.1-2), the applicant explained that toxicological characterization related to VP44469 exposure had been performed in these studies.

5.8.5 Toxicity evaluation of impurities

Impurities that may be present in the drug substance or the drug product, or those that may be formed during their manufacturing process or storage were evaluated using published information and an *in silico* mutagenesis model in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M7 guideline. Impurity A, Impurity B, Impurity C, Impurity D

([redacted]), Impurity E, and Impurity F ([redacted]) were evaluated using the Ames test. These impurities were determined to be non-mutagenic (CTD 4.2.3.7.6-2 to 4.2.3.7.6-6, and 4.2.3.7.6-12). The known mutagenic carcinogen Impurity G ([redacted]) is controlled below the acceptable intake based on the risk assessment of the substance.

5.R Outline of the review conducted by PMDA

5.R.1 Effect on the gastrointestinal system

Toxicity findings suggesting an effect on the gastrointestinal system were observed in non-clinical studies [see Section 5.2].

The applicant's explanation about the effect of maribavir on the gastrointestinal system:

Changes in stool properties or mucosal hyperplasia in the digestive tract were observed at exposure levels equal to or below the human exposure level in repeated-dose toxicity studies in rats and cynomolgus monkeys, and the mechanism of their onset has not been fully clarified. However, the gastrointestinal safety and tolerability of maribavir in humans are considered acceptable for the following reasons: Regarding adverse events related to gastrointestinal disorders observed with maribavir in foreign phase III studies (Studies 302 and 303) and the Japanese phase III study (Study 3001), the incidence was similar in the maribavir group and the comparator group[27)] in Studies 302 and 303, even when assessed by seriousness (serious or non-serious); there were no events that resulted in death in either study; all of the serious adverse events, for which a causal relationship to the study drug was not ruled out, resolved; no serious adverse events for which a causal relationship to the study drug was not ruled out were observed in Study 3001.

PMDA's view:

The gastrointestinal mucosal toxicity findings observed in the repeated-dose toxicity studies of maribavir were common to rats and cynomolgus monkeys and occurred at exposure levels equal to or below the human exposure level, and the mechanism of their onset remains unclear. Therefore, maribavir may also have a potential risk in humans. However, in view of the Japanese and foreign clinical study results, the applicant's position that the gastrointestinal safety and tolerability of maribavir when administered to humans are acceptable is deemed acceptable.

5.R.2 Effect on red blood cell parameters

The applicant's explanation:

Although toxicity findings suggesting an effect on red blood cell parameters were observed in non-clinical studies [see Section 5.2], there were very few adverse events and no adverse drug reactions related to red blood cell parameters in Japanese and foreign clinical studies. Therefore, maribavir is unlikely to exert an effect of clinical concern on red blood cell parameters, and specific precautionary measures are considered unnecessary.

27) The VGCV group in Study 302; the IAT group in Study 303.

PMDA's view:
Since the decreases in red blood cell parameters observed in the repeated-dose toxicity studies of maribavir were common to rats and cynomolgus monkeys and occurred at exposure levels around the human exposure, maribavir may have a potential risk in humans. However, since there were very few such events in Japanese and foreign clinical studies, the applicant's position that specific precautionary measures are unnecessary at present is deemed acceptable.

5.R.3 Carcinogenicity

In the carcinogenicity study of maribavir in mice, the incidence of hemangioma and angiosarcoma increased at an exposure approximately 4.0 times the human exposure.
The applicant's explanation:

Induction of hypoxia or changes such as macrophage activation (*Toxicol Sci*. 2009;111(1):4-18), which are considered as the starting point of the non-genotoxic induction mechanism of angiosarcoma, were not observed in the 13-week repeated-dose toxicity study (CTD 4.2.3.2-2) or the carcinogenicity study (CTD 4.2.3.4.1-1) of maribavir in mice, and the mechanism of its development was unclear. In addition, hemangioma or angiosarcoma was not observed in the 13-week repeated-dose toxicity study in mice (19-20 weeks of age at the time of necropsy). When the estimated age of onset of hemangioma or angiosarcoma (68-69 weeks) in the carcinogenicity study in mice is converted to human years, the tumor would have developed after an administration period corresponding to at least several decades in humans. However, it has been reported that the incidence of spontaneous angiosarcoma is much lower in humans (<0.001%) than in mice (2%-5%) and the mode of development of angiosarcoma differs among different animal species (*Toxicol Sci*. 2009;111(1):4-18).

Maribavir is anticipated to be used for approximately 2 weeks to several months for the treatment of CMV disease in clinical practice. The total duration of administration is expected to be a maximum of appropriately 1 year, even if CMV disease relapses. Therefore, in the actual clinical setting, maribavir is unlikely to be administered for such a long period that hemangioma or angiosarcoma may develop.

In view of the above, although the mechanism of development of hemangioma and angiosarcoma resulting from maribavir treatment is unclear, the carcinogenic risk is unlikely to occur in humans from the viewpoints of treatment duration and species difference.

PMDA's view:
Taking the timing of development of the tumors into account, the applicant's explanation that hemangioma and angiosarcoma are unlikely to develop during the standard treatment duration of maribavir, is understandable. However, the safety margin between the non-carcinogenic dose and human exposure is insufficient, and the relevance of the events to humans has not been clarified based on the mechanism of development. Therefore, information should be provided to healthcare professionals by addressing the increased incidence of hemangioma and angiosarcoma in non-clinical studies in the package insert.

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

The applicant submitted the results of biopharmaceutic studies of maribavir, including a food effect study.

Five formulations were mainly used in the clinical studies of maribavir (Capsule Formulation, and Tablet Formulations I to IV). Of them, Tablet Formulation IV, which was used in the Japanese phase III study (Study 3001), foreign phase III studies (Studies 302 and 303), and the food effect study (Study TAK-620-1025), was regarded as the proposed commercial formulation. Table 29 shows the clinical studies conducted using these formulations.

Human plasma and urinary concentrations of maribavir and VP44469 were measured by HPLC or LC/MS/MS (LLOQ = 5-200 ng/mL for both maribavir and VP44469), and radioactivity concentrations were measured by accelerator mass spectrometry.

Table 29. Formulations used in the development of maribavir and clinical studies conducted using these formulations

Dosage form	Maribavir content	Clinical studies
Capsule Formulation	12.5 mg	Phase I: Study CMAB1001
	100 mg	Phase I: Studies CMAB1001, CMAB1002, CMAA1003, and CMAA1004
Tablet Formulation I	100 mg	Phase I: Studies 1263-100, 1263-101, 1263-102, 1263-103, and 1263-104
Tablet Formulation II	200 mg	Phase I: Studies 1263-104, 1263-105, 1263-107, 1263-108, and 1263-110 Phase II: Studies 202 and 203
Tablet Formulation III	100 mg	Phase I: Studies 1263-108 and 1263-109
Tablet Formulation IV	200 mg	Phase I: Studies SHP620-115, TAK-620-1019, TAK-620-1020, and TAK-620-1025 Phase III: Studies 3001, 302, and 303

6.1.1 Food effect study (Reference CTD 5.3.1.1-1: Study TAK-620-1025 [May to July 2022])

A 6-group 3-period crossover study was conducted to investigate the PK of maribavir following a single oral dose of 400 mg of the proposed commercial formulation (Tablet Formulation IV) under fasted conditions, after intake of a low-fat diet,[28)] or after intake of a high-fat diet[29)] in non-Japanese healthy adults (30 subjects included in PK analysis). The results are as follows: The geometric least squares mean ratios [90% confidence interval (CI)] of the plasma C_{max}, AUC_{inf}, and AUC_{last} of maribavir when administered after intake of a low-fat diet or after intake of a high-fat diet to those when maribavir was administered under fasted conditions were 0.77 [0.72, 0.82], 0.85 [0.81, 0.88], and 0.84 [0.81, 0.88], respectively, for administration after intake of a low-fat diet, and 0.72 [0.67, 0.76], 0.88 [0.84, 0.92], and 0.87 [0.84, 0.91], respectively, for administration after intake of a high-fat diet. Plasma exposure to maribavir (C_{max}, AUC_{inf}, and AUC_{last}) tended to decrease following administration after a meal. However, the efficacy of maribavir was demonstrated in the foreign phase III study (Study 303) in which maribavir was administered without a defined relationship between meal conditions and maribavir administration [see Section 7.2.1]. The applicant therefore explained that the decrease in plasma exposure to maribavir following administration after a meal would not become a clinically relevant problem.

[28)] Total calories were 400 to 500 kcal, including 100 to 125 kcal of lipids.
[29)] Total calories were 800 to 1,000 kcal, including 250 kcal of carbohydrates, 150 kcal of proteins, and 500 to 600 kcal of lipids.

6.2 Clinical pharmacology

The applicant submitted the results of clinical pharmacology studies including studies in healthy subjects, patients with CMV disease, and subjects with hepatic or renal impairment, pharmacokinetic interaction studies, a QT/QTc assessment study, and a population pharmacokinetic (PPK) analysis. Unless otherwise specified, the dose of each formulation is expressed as the dose of maribavir, and the value of each PK parameter is expressed as the mean or the mean ± standard deviation.

6.2.1 Investigations in healthy subjects

6.2.1.1 Foreign phase I study (CTD 5.3.3.3-1: Study TAK-620-1020 [August to November 2020]. Reference CTD 5.3.3.1-1: Study CMAB1001 [[redacted] 19[redacted] to [redacted] 19[redacted]])

Table 30 shows the PK parameters of maribavir and VP44469 following a single oral dose of maribavir 50 to 1,600 mg under fasted conditions in non-Japanese healthy adult males (10 subjects/group included in PK analysis) and following a single oral dose of maribavir 200 to 800 mg under fasted conditions in Japanese or non-Japanese healthy adults (12 subjects/group included in PK analysis). The C_{max} and AUC_{inf} of maribavir and VP44469 increased in a nearly dose-proportional manner in both Japanese and non-Japanese subjects. The geometric least squares mean ratios [90% CI] of exposure (C_{max} and AUC_{inf}) in Japanese subjects to that in non-Japanese subjects[30)] following a single oral dose of maribavir 400 mg were 1.10 [0.92, 1.33] and 1.25 [0.98, 1.60], respectively, for maribavir, and 1.01 [0.85, 1.19] and 1.06 [0.89, 1.26], respectively, for VP44469.

The protein binding rates (ultrafiltration method) of maribavir and VP44469 following a single oral dose of maribavir 200 or 800 mg in non-Japanese subjects were 98.7% at both doses for maribavir, and 89.7 and 92.4%, respectively, for VP44469.

Table 30. PK parameters of maribavir and VP44469 following a single oral dose of maribavir

Subjects (Study)	Dose (mg)	N	Analyte	t_{max} (h)	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
Non-Japanese (CMAB1001)	50	10	Maribavir	1.0 [0.5, 1.5]	2.66 ± 0.56	10.8 ± 3.4	3.28 ± 0.61	5.02 (27.9)
			VP44469	1.5 [1.0, 4.0]	0.19 ± 0.04	1.85 ± 0.63	6.31 ± 2.93	-
	100	10	Maribavir	2.3 [0.5, 5.0]	3.32 ± 1.22	16.3 ± 4.5	3.01 ± 0.46	6.46 (20.7)
			VP44469	3.0 [1.0, 6.0]	0.32 ± 0.08	2.90 ± 0.38	4.96 ± 0.69	-
	200	10	Maribavir	1.3 [1.0, 4.0]	7.45 ± 2.89	34.2 ± 16.9	3.64 ± 1.09	6.69 (30.4)
			VP44469	2.0 [1.0, 5.0]	0.65 ± 0.23	6.02 ± 1.09	5.23 ± 1.44	-
	400	10	Maribavir	1.8 [1.0, 3.0]	16.7 ± 5.7	97.8 ± 28.6	3.91 ± 0.78	4.39 (27.2)
			VP44469	3.0 [1.0, 5.0]	1.37 ± 0.48	16.2 ± 5.2	5.95 ± 1.22	-
	800	10	Maribavir	1.5 [1.0, 4.2]	26.4 ± 6.9	183 ± 69	4.04 ± 1.02	4.84 (31.1)
			VP44469	3.0 [2.0, 5.0]	2.11 ± 0.59	27.5 ± 5.7	6.65 ± 3.38	-
	1600	10	Maribavir	2.0 [1.0, 3.0]	48.8 ± 7.9	437 ± 163	4.80 ± 1.53	4.12 (35.7)
			VP44469	4.0 [3.0, 12]	3.64 ± 0.57	60.0 ± 13.2	7.18 ± 3.07	-
Japanese (TAK-620-1020)	200	12	Maribavir	1.0 [0.5, 4.0]	9.46 ± 2.88	46.4 ± 18.8	5.64 ± 1.66	5.00 (38.9)
			VP44469	2.0 [1.0, 5.0]	0.871 ± 0.224	8.33 ± 2.15	6.58 ± 1.73	-
	400	12	Maribavir	1.3 [0.5, 4.0]	18.0 ± 4.5	102 ± 36	5.48 ± 1.80	4.39 (36.7)
			VP44469	2.0 [1.0, 5.0]	1.43 ± 0.39	16.0 ± 3.5[a)]	7.34 ± 2.04[a)]	-
	800	12	Maribavir	2.5 [1.0, 4.0]	27.5 ± 9.4	212 ± 87	5.65 ± 1.16	4.43 (42.0)
			VP44469	3.0 [1.5, 5.0]	2.65 ± 1.06	30.1 ± 7.0[b)]	6.88 ± 1.86[b)]	-
Non-Japanese (TAK-620-1020)	400	12	Maribavir	1.8 [0.5, 4.0]	16.3 ± 4.2	80.9 ± 22.8	4.81 ± 1.39	5.49 (41.8)
			VP44469	2.0 [1.5, 5.0]	1.41 ± 0.32	15.2 ± 4.0[a)]	5.98 ± 1.00[a)]	-

t_{max}, median (range); CL/F, mean (%CV); -. not calculated.
a) N = 11; b) N = 8.

[30)] Non-Japanese healthy adults matched to the Japanese healthy adults in terms of sex, age (±10 years), and body mass index (BMI) (±15%).

6.2.1.2 Mass balance study (Reference CTD 5.3.3.1-2: Study 1263-106 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Mass balance was investigated in non-Japanese healthy adults (6 subjects included in PK analysis) who received a single oral dose of citric acid solution containing ^{14}C-labeled maribavir 400 mg using a nasogastric tube.

The maximum plasma radioactivity concentration was observed at 1 to 3 hours post-dose, and by 24 hours post-dose, the plasma radioactivity concentration decreased to approximately 1/30 of the maximum concentration. Up to 24 hours post-dose, maribavir and VP44469 were mainly detected in plasma (at 88% and 12%, respectively, of the total radioactivity in plasma).

By 144 hours post-dose, 61.2% and 13.6% of the administered radioactivity were excreted in urine and feces, respectively. The radioactivity excreted in urine by 48 hours post-dose accounted for 60.4% of the administered radioactivity, and maribavir and VP44469 were detected at 1.8% and 34.0%, respectively, of the administered radioactivity. The radioactivity excreted in feces by 96 hours post-dose accounted for 13.1% of the administered radioactivity, and maribavir and VP44469 were detected at 5.7% and 7.2%, respectively, of the administered radioactivity.

The above results and the *in vitro* metabolism study results [see Section 4.3.1] suggested that maribavir is mainly metabolized in the liver in humans, converting into VP44469 and other metabolites, and that maribavir is mainly excreted as metabolites in urine.

6.2.2 Investigations in patients

6.2.2.1 Foreign phase II study (CTD 5.3.5.2-1: Study 202 [July 2012 to December 2014])

Table 31 shows the PK parameters of maribavir following multiple oral doses of maribavir 400, 800, or 1,200 mg twice daily in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance) (non-Japanese subjects, aged ≥12 years; 33 subjects included in the non-compartmental PK analysis). The C_{max} and AUC_{last} of maribavir[31)] increased in a less-than dose-proportional manner.

Table 31. PK parameters of maribavir following multiple oral doses of maribavir

Dose	N	Measurement day[a)]	t_{max} (h)	C_{max} (μg/mL)	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)
400 mg BID	12	Day 8	3.0 [0.9, 12]	18.5 ± 7.4	100 ± 50	5.56 ± 3.85[b)]
	8	Day 28	1.5 [1.0, 3.2]	17.8 ± 8.4	90.9 ± 64.3	4.32 ± 1.25[c)]
800 mg BID	10	Day 8	1.5 [0, 8.0]	35.1 ± 12.0	179 ± 70	6.08 ± 3.51[d)]
	10	Day 28	3.0 [1.0, 8.0]	25.0 ± 9.7	139 ± 61	6.34 ± 1.41[c)]
1200 mg BID	8	Day 8	3.0 [0, 6.0]	45.1 ± 21.2	264 ± 147	7.77 ± 3.59[e)]
	6	Day 28	3.5 [1.8, 4.1]	35.6 ± 25.8	207 ± 161	5.33 ± 2.55[e)]

t_{max}, median (range).

a) The allowable time window for measurement was ±1 day for Day 8 and ±2 for Day 28. No. of subjects analyzed: b) N = 6; c) N = 5s; d) N = 7; e) N = 3.

31) While the dose of marivavir per administration was escalated by 3-fold, i.e., from 400 mg to 1,200 mg, the C_{max} and AUC_{last} of maribavir increased by 2.4- and 2.6-fold, respectively, on Day 8, and by 2.0- and 2.3-fold, respectively, on Day 28.

6.2.3 Investigation of intrinsic factors

6.2.3.1 Study in subjects with hepatic impairment (Reference CTD 5.3.3.3-3: Study 1263-103 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Table 32 shows the PK parameters of maribavir and VP44469 following a single oral dose of maribavir 200 mg in non-Japanese adults with normal hepatic function and non-Japanese adults with moderate hepatic impairment (Child-Pugh class B). The plasma protein-unbound fraction of maribavir was 1.5% and 1.3% in subjects with normal hepatic function and subjects with moderate hepatic impairment, respectively. The C_{max} and AUC_{inf} of maribavir (bound + unbound) in subjects with moderate hepatic impairment tended to be higher than those in subjects with normal hepatic function. However, according to the applicant, since the C_{max} and AUC_{inf} of maribavir (unbound) were generally similar to those in subjects with normal hepatic function, dose adjustment of maribavir is unnecessary for patients with mild or moderate hepatic impairment. However, given that no studies in subjects with severe hepatic impairment (Child-Pugh class C) were conducted, and that maribavir is considered to be mainly metabolized in the liver [see Sections 4.3.1 and 6.2.1.2], the applicant explained that precautions would be provided in the package insert to warn that exposure to maribavir may increase in patients with severe hepatic impairment.

Table 32. PK parameters of maribavir and VP44469 by hepatic function following a single oral dose of maribavir

Hepatic function	N	Analyte	Plasma protein binding	C_{max} (μg/mL)		AUC_{inf} (μg·h/mL)	
				Geometric mean	Least squares mean ratio [90% CI] (impairment/normal function)	Geometric mean	Least squares mean ratio [90% CI] (impairment/normal function)
Normal function[a)]	10	Maribavir	Bound + unbound	9.45		62.3	
			Unbound	0.139		0.918	
		VP44469	Bound + unbound	0.85		9.54	
Moderate impairment	10	Maribavir	Bound + unbound	12.7	1.35 [1.09, 1.66]	78.6	1.26 [0.89, 1.79]
			Unbound	0.153	1.10 [0.89, 1.36]	0.946	1.03 [0.73, 1.46]
		VP44469	Bound + unbound	1.01	1.19 [0.84, 1.69]	12.5	1.31 [1.01, 1.70]

a) Subjects with normal hepatic function generally matched to the subjects with moderate hepatic impairment in terms of age, body weight, sex, and smoking status.

6.2.3.2 Study in subjects with renal impairment (Reference CTD 5.3.3.3-2: Study 1263-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Table 33 shows the PK parameters of maribavir and VP44469 following a single oral dose of maribavir 400 mg in non-Japanese adults with normal renal function (CLcr >80 mL/min) or mild (CLcr 50-80 mL/min), moderate (CLcr 30-<50 mL/min), or severe (CLcr <30 mL/min) renal impairment. The plasma protein-unbound fraction of maribavir by renal function was 1.1% for normal function, 1.2% for mild and moderate impairment, and 1.5% for severe impairment.

While the C_{max} and AUC_{inf} of maribavir were generally similar in subjects with normal renal function and subjects with mild to severe renal impairment, the C_{max} and AUC_{inf} of VP44469 were higher in subjects with mild to severe renal impairment than in subjects with normal renal function. Since the safety of multiple dose administration of maribavir 1,200 mg twice daily, which is 3-fold the dose specified in the proposed dosage and administration (400 mg twice daily), was confirmed in foreign phase II studies (Studies 202 and 203), the

increase in plasma exposure to VP44469 in patients with renal impairment would not become a clinically relevant problem, and dose adjustment of maribavir is unnecessary, according to the applicant.

Table 33. PK parameters of maribavir and VP44469 by renal function following a single oral dose of maribavir

Renal function	N	Analyte	Plasma protein binding	C_{max} (μg/mL)		AUC_{inf} (μg·h/mL)	
				Geometric mean	Least squares mean ratio [90% CI] (impairment/normal function)	Geometric mean	Least squares mean ratio [90% CI] (impairment/normal function)
Normal function[a)]	12	Maribavir	Bound + unbound	21.9		128	
			Unbound	0.236		1.45	
		VP44469	Bound + unbound	1.75		21.8	
Mild or moderate impairment	10	Maribavir	Bound + unbound	21.0	0.959 [0.767, 1.20]	138	1.08 [0.81, 1.46]
			Unbound	0.246	1.04 [0.764, 1.43]	1.62	1.11 [0.817, 1.51]
		VP44469	Bound + unbound	2.38	1.37 [1.09, 1.71]	41.0	1.88 [1.51, 2.35]
Severe impairment	8	Maribavir	Bound + unbound	20.3	0.930 [0.732, 1.18]	123	0.961 [0.701, 1.32]
			Unbound	0.289	1.23 [0.888, 1.69]	1.74	1.20 [0.872, 1.64]
		VP44469	Bound + unbound	2.37	1.36 [1.07, 1.72]	45.4	2.08 [1.65, 2.64]

a) Subjects with normal renal function generally matched to the subjects with renal impairment in terms of age, body weight, and sex.

6.2.4 Investigation of pharmacokinetic interactions[32)]

Pharmacokinetic interactions between maribavir and concomitant drugs were investigated. Table 34 and Table 35 show the results.

Table 34. Effect of concomitant drugs on the PK parameters of maribavir

Dosage regimen of maribavir (p.o. for all regimens)	Concomitant drug[a)]	Dosage regimen of concomitant drug (p.o. for all regimens)	N (with/without concomitant drug)	Analyte	Least squares mean ratio [90% CI] (with/without concomitant use)		
					C_{max}	AUC_{inf}	C_{trough}
400 mg, single dose	Ketoconazole	400 mg, single dose	19/19	Maribavir	1.10 [1.01, 1.19]	1.53 [1.44, 1.63]	-
				VP44469	0.598 [0.546, 0.656]	1.15 [1.08, 1.23]	-
400 mg BID on Day 1 and Day 2 400 mg QD on Day 3	Rifampicin	600 mg QD, multiple doses	14/14	Maribavir	0.612 [0.523, 0.717]	0.398 [0.361, 0.440][b)]	0.183 [0.135, 0.247]
				VP44469	1.41 [1.31, 1.52]	1.00 [0.964, 1.05][b)]	0.612 [0.535, 0.700]
100 mg, single dose	Aluminum hydroxide and magnesium hydroxide	800 mg, single dose, for both	15/15	Maribavir	0.837 [0.747, 0.939]	0.891 [0.828, 0.958]	-
				VP44469	0.866 [0.755, 0.967]	1.03 [0.900, 1.18]	-

-, not calculated.

a) Ketoconazole is a CYP3A4/P-gp inhibitor; rifampicin is a CYP3A4 inducer; aluminum hydroxide and magnesium hydroxide are antacids.

b) AUC_{last}.

[32)] Reference CTD 5.3.1.1-3: Study 1263-109 [[redacted] to [redacted]]. Reference CTD 5.3.3.4-1: Study 1263-100 [[redacted] to [redacted]]. Reference CTD 5.3.3.4-2: Study 1263-102 [[redacted] to [redacted]]. Reference CTD 5.3.3.4-3: Study 1263-105 [[redacted] to [redacted]]. Reference CTD 5.3.3.4-4: Study 1263-107 [[redacted] to [redacted]]. Reference CTD 5.3.3.4-5: Study 1263-110 [[redacted] to [redacted]]. Reference CTD 5.3.3.4-6: Study SHP620-115 [July 2016 to September 2016].
Study 1263-105 was conducted in patients with stable renal graft function and maintained on tacrolimus BID after renal transplantation, and the other clinical studies were conducted in healthy adults.

Table 35. Effect of maribavir on the PK parameters of concomitant drugs

Dosage regimen of maribavir (p.o. for all regimens)	Concomitant drug[a)]	Dosage regimen of concomitant drug (p.o. for all regimens)	N (with/without concomitant drug)	Analyte	Least squares mean ratio [90% CI] (with/without concomitant use)	
					C_{max}	AUC_{inf}
400 mg BID	Digoxin	0.5 mg, single dose	18/18	Digoxin	1.25 [1.13, 1.38]	1.21 [1.10, 1.32]
400 mg BID	Dextromethorphan	30 mg, single dose	18/18	Dextromethorphan	0.944 [0.778, 1.14]	0.882 [0.696, 1.12][b)]
				Dextrorphan	0.943 [0.883, 1.01]	0.973 [0.949, 0.998][b)]
400 mg BID on Day 1 to Day 6 400 mg QD on Day 7	Tacrolimus	Maintenance dose, BID	20/20	Tacrolimus	1.38 [1.20, 1.57]	1.51 [1.39, 1.65][c)]
	Voriconazole	200 mg BID[d)]	19/19	Voriconazole	0.996 [0.865, 1.15]	0.933 [0.830, 1.05][b)]
				Voriconazole-N-oxide	1.01 [0.932, 1.08]	1.04 [0.992, 1.10][b)]
400 mg BID	Warfarin	10 mg, single dose (with vitamin K 10 mg)	16/16	S-warfarin	1.04 [0.959, 1.12]	1.01 [0.953, 1.07]
400 mg BID	Midazolam	0.075 mg/kg, single dose	16/16	Midazolam	0.820 [0.699, 0.961]	0.891 [0.794, 0.998]
			16/16	1-Hydroxymidazolam	0.984 [0.712, 1.26]	1.06 [0.912, 1.21]
400 mg BID	Caffeine	2 mg/kg, single dose	15/15	Caffeine metabolites in urine[e)]	Urinary concentration ratio up to 12 hours post-dose	
					0.862 [0.803, 0.920]	

a) Digoxin is a substrate of P-gp; dextromethorphan is a substrate of CYP2D6; tacrolimus is a substrate of CYP3A4 and P-gp; voriconazole is a substrate of CYP2C9, CYP2C19, and CYP3A4; caffeine is a substrate of CYP1A2; warfarin is a substrate of CYP2C9; midazolam is a substrate of CYP3A4. Digoxin and dextromethorphan were administered simultaneously in the clinical drug interaction study (Study SHP620-115). Midazolam was administered within 1 hour after maribavir administration in the clinical drug interaction study (Study 1263-100). Caffeine and warfarin were administered simultaneously with omeprazole 40 mg and dextromethorphan 30 mg within 3 hours after midazolam administration.

b) AUC_{last}. c) AUC_{τ}. d) 400 mg BID on Day 1, and 200 mg QD on the last day of dosing. e) The urinary concentration ratio of caffeine metabolites was calculated using the parameters presented in the following formula: (1-Methylxanthine + 1-methyluric acid + 5-acetylamino-6-formylamino-3-methyluracil) / 1,7-dimethyluric acid. The urinary concentration ratio of caffeine metabolites is positively correlated with the systemic clearance of caffeine (correlation coefficient, 0.77), and is considered as an indicator of CYP1A2 activity (*Pharmacogenetics*. 1994;4:117-124 and C*ancer Epidemiol Biomakers Prev*. 1992;8:159-166).

6.2.5 QT/QTc assessment study (Reference CTD 5.3.4.1-1: Study 1263-108 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The effect on the QT/QTc interval was investigated in non-Japanese healthy adults (52 subjects included in QT/QTc assessment) who received a single oral dose of placebo or maribavir 100 mg or 1,200 mg, with moxifloxacin 400 mg (as a single oral dose) as a positive control (4-group 4-period crossover study, with a washout period of 4 to 14 days for each period). The maximum difference [90% CI] in the change from baseline of the QT rate-corrected individually with placebo QT/RR interval (QTcIb) following administration of maribavir 100 mg or 1,200 mg compared with placebo administration (ΔΔQTcIb) was 3.63 ms [0.98, 6.27] (maribavir 100 mg, at 22 hours post-dose) and 2.57 ms [−0.07, 5.21] (maribavir 1,200 mg, at 3 hours post-dose). The upper limit of the 90% CI was below 10 ms at both doses. The maximum ΔΔQTcIb [90% CI] of the positive control was 9.16 ms [6.53, 11.79] (at 3 hours post-dose).

6.2.6 PPK analysis (Reference CTD 5.3.3.5-2 and 5.3.3.5-5)

A PPK analysis (NONMEM version 7.5.1) was performed using plasma maribavir concentration data from 14 clinical studies in healthy adults, patients with hepatic impairment, patients with renal impairment, patients

after renal transplantation, and HSCT or SOT recipients with CMV disease[33)] (930 subjects [7,431 measurement points]). Subsequently, the PPK model was updated using newly obtained plasma maribavir concentration data (41 subjects from the Japanese phase III study (Study 3001) [176 measurement points]). The PK of maribavir was described by a 2-compartment model with first-order absorption plus lag time, and the following factors were selected as covariates for individual PK parameters[34)]:

- Concomitant use of proton pump inhibitors, for relative bioavailability (BA) (F)
- Maribavir dose and concomitant use of proton pump inhibitors, for absorption rate constant (K_a)
- Body weight, CMV category, concomitant use of strong CYP3A4 inhibitors, concomitant use of strong CYP3A4 inducers, and Japanese (Japanese/non-Japanese), for apparent systemic clearance (CL/F)
- Body weight, for apparent volume of distribution of the central compartment (V_c/F), apparent volume of distribution of the peripheral compartment (V_p/F), and apparent intercompartmental clearance (Q/F)

Table 36 shows the estimated PK parameters of maribavir (at steady state) in HSCT or SOT recipients with CMV disease, which were calculated using the updated PPK model. Plasma exposure to maribavir (C_{max}, AUC_τ, etc.) was higher in Japanese subjects than in non-Japanese subjects. The applicant explained that this result is considered attributable to lower body weight in Japanese subjects than in non-Japanese subjects and the higher proportion of Japanese subjects with hepatic impairment[35)]; however, the estimated exposure is clinically insignificant because (i) it falls within the exposure range following administration of maribavir 1,200 mg BID in Studies 202 and 203 and (ii) the safety has been confirmed in this exposure range.

Table 36. PK parameters of maribavir estimated using a PPK model in HSCT or SOT recipients with CMV disease (steady state)

Studies	Dose (mg)	No. of subjects evaluated	C_{max} (μg/mL)	C_{trough} (μg/mL)	AUC_τ (μg·h/mL)	$t_{1/2}$ (h)
Studies 202, 203, 302, and 303 (non-Japanese)	400 mg BID	724	20.2 (35.5)	5.52 (86.6)	143 (48.6)	6.81 (41.2)
Study 3001 (Japanese)	400 mg BID	41	29.1 (40.6)	9.89 (97.8)	221 (57.1)	8.72 (55.4)
Studies 202 and 203 (non-Japanese)	1,200 mg BID	232	58.8 (35.4)	15.5 (84.3)	408 (48.2)	6.83 (47.3)

Geometric mean (CV%)

33) Phase I studies in healthy adults (Studies 1263-100, 1263-102, 1263-104, 1263-109, 1263-110, SHP620-115, and TAK-620-1020), phase I study in stable patients after renal transplantation (Study 1263-105), phase I study in subjects with hepatic impairment (Study 1263-103), phase I study in subjects with renal impairment (Study 1263-101), and phase II and phase III studies in HSCT or SOT recipients with CMV disease (Studies 202, 203, 302, and 303).

34) The following factors were assessed as candidate covariates: body weight, height, BMI, age, sex, race or ethnicity (Asian/Black/ Caucasian/Others), Japanese (Japanese/non-Japanese), Chinese (Chinese/non-Chinese), hepatic function (no chronic hepatic disease or hepatic impairment/Child Pugh class A/Child Pugh class B), health status (healthy/CMV patient/hepatic impairment/mild or moderate renal impairment/severe renal impairment/stable after renal transplantation), type of transplantation (no transplantation/HSCT/SOT), plasma CMV DNA level at baseline, status of CMV mutations, CMV category (no infection/asymptomatic CMV viremia/symptomatic CMV disease/organ CMV disease or tissue-invasive CMV disease), positioning of treatment of CMV disease (refractory to existing treatments/untreated), anti-lymphocyte antibody use at baseline, previous use of CMV drugs, gastrointestinal graft-versus-host disease (absent/mild/moderate/severe), diarrhea, vomiting, concomitant use of CYP3A4 inducers, concomitant use of proton pump inhibitors, concomitant use of H_2 receptor inhibitors, concomitant use of antacids, maribavir dose, meal (fasted/non-fasted), drug product batch, and effect of tablet crushing.

35) Body weight (mean ± standard deviation) was 57.5 ± 10.7 kg in Japanese subjects and 73.1 ± 17.8 kg in non-Japanese subjects. The percentage of subjects with hepatic impairment was 22.0% (9/41 subjects) in Japanese subjects and 5.0% (36/724 subjects) in non-Japanese subjects.

6.R Outline of the review conducted by PMDA

6.R.1 Drug interactions

6.R.1.1 Effect of concomitant drugs on the PK of maribavir

Maribavir is mainly metabolized by CYP3A4 and is subject to P-gp-mediated transport.

PMDA's view about the effect on the PK parameters of maribavir when concomitantly used with CYP3A4 inhibitors or inducers, or P-gp inhibitors and the need to provide precautions regarding concomitant use with these drugs:

Concomitant use with CYP3A4 inhibitors and P-gp inhibitors

The results of the clinical drug interaction study of concomitant use of maribavir with oral ketoconazole, a CYP3A4 and P-gp inhibitor, showed that the AUC_{inf} of maribavir increased by 1.53-fold when concomitantly used with ketoconazole, compared to that of maribavir administered alone [see Section 6.2.4]. However, in Studies 202 and 203, the safety of maribavir was confirmed up to 3-fold (maribavir 1,200 mg BID) the dose specified in the proposed dosage and administration (maribavir 400 mg BID), and the safety profile was acceptable [see Section 7.R.3]. PMDA therefore considered that the need to provide precautions regarding concomitant use of maribavir with CYP3A4 inhibitors and P-gp inhibitors is low.

Concomitant use with CYP3A4 inducers

The results of the clinical drug interaction study of maribavir involving concomitant use with rifampicin, a strong CYP3A4 inducer, showed that the AUC_{last} and C_{trough} of maribavir decreased by 0.398-fold and 0.183-fold, respectively, when concomitantly used with rifampicin, compared to those of maribavir administered alone [see Section 6.2.4]. Since the efficacy of maribavir administered at lower doses than the dose specified in the proposed dosage and administration (400 mg BID) was not investigated in clinical studies, maribavir is unlikely to be effective when concomitantly used with a CYP3A4 inducer, PMDA therefore considered that precautions should be provided in the package insert regarding concomitant use of maribavir with CYP3A4 inducers, as described below.

- Even when maribavir is administered at 1,200 mg BID (3-fold the dose specified in the proposed dosage and administration), which was used in Studies 202 and 203, in the presence of concomitant rifampicin, the plasma maribavir concentration is predicted to be lower than the plasma C_{trough} of maribavir at the proposed dosage and administration (400 mg BID) without rifampicin use. For this reason, an appropriate dose of maribavir when concomitantly used with rifampicin cannot be established. Therefore, concomitant use of maribavir and rifampicin should be contraindicated. Concomitant use with food containing St. John's Wort, a strong CYP3A4 inducer, should also be contraindicated.
- Concomitant use with other moderate to strong CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine, efavirenz, rifabutin, etc.) is also predicted to decrease plasma exposure to maribavir, which may attenuate the efficacy of maribavir. For this reason, concomitant use of maribavir with these drugs is not recommended, and change to alternative drugs should be considered. However, if concomitant use with these CYP3A4 inducers is unavoidable, dose increase of maribavir up to 1,200 mg BID may be considered, in light of the following points:
  - Other moderate to strong CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine, efavirenz,

rifabutin, etc.) are not as potent as rifampicin.[36] Therefore, if the dose of maribavir is increased to 1,200 mg BID in the presence of concomitant use with these CYP3A4 inducers, the resulting exposure may generally be similar to or even higher than the plasma C_{trough} of maribavir at the proposed dosage and administration (maribavir 400 mg BID) without concomitant use.

- In Studies 202 and 203, the safety of maribavir was confirmed up to 3-fold (maribavir 1,200 mg BID) the dose specified in the proposed dosage and administration (maribavir 400 mg BID), and the safety profile was acceptable [see Section 7.R.3].

Since information on the concomitant use of maribavir with CYP3A4 inducers is limited, such information should be continuously collected even in the post-marketing setting, and new findings should be provided to healthcare professionals immediately when they become available.

6.R.1.2 Effect of maribavir on the PK of concomitant drugs

The applicant's explanation about the effect of maribavir on the PK of concomitant drugs:

Administration of maribavir at the proposed dosage and administration (400 mg BID) increased the plasma AUC of digoxin (substrate of P-gp) and tacrolimus (substrate of CYP3A4 and P-gp) by 1.21- and 1.51-fold, respectively [see Section 6.2.4]. Therefore, precautions will be provided in the package insert regarding the concomitant use with these narrow therapeutic index substrate drugs of P-gp (digoxin) and CYP3A4 and P-gp (tacrolimus).

Maribavir inhibited BCRP in *in vitro* studies [see Section 4.5.4]. Although no clinical drug interaction studies on the concomitant use of maribavir with BCRP substrates were conducted, the effect of maribavir at the proposed dosage and administration (400 mg BID) on the PK of BCRP substrate drugs (rosuvastatin and salazosulfapyridine) was investigated using a physiologically based pharmacokinetic (PBPK) model.[37] As a result, the geometric mean ratios of the plasma AUC of rosuvastatin and salazosulfapyridine when concomitantly used with maribavir to that when each drug was administered alone were estimated to be 2.15 to 2.94 and 3.15 to 3.60, respectively. Therefore, precautions will also be provided in the package insert regarding the concomitant use with these BCRP substrate drugs.

PMDA's view:

The applicant's proposal to provide precautions in the package insert regarding the concomitant use with narrow therapeutic index substrate drugs of P-gp (digoxin) and CYP3A4 and P-gp (tacrolimus) is acceptable. For concomitant use of maribavir with BCRP substrate drugs, since exposure to BCRP substrate drugs (rosuvastatin and salazosulfapyridine) was predicted to increase, the applicant's proposal to provide

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[36] *Drug Metab Pharmacokinet*. 2021; 41:100414, *Clin Pharmacokinet*. 2008;10:669-680.

[37] Simcyp Version 19 release 1 was employed in the analysis using a PBPK model. The Advanced Dissolution, Absorption and Metabolism model was selected as the absorption model, and the Full PBPK model as the distribution model of maribavir. The absorption ratio (fraction absorbed [fa]) was set as 0.9 based on the mass balance study [see Section 6.2.1.2]. The unbound fraction in gastrointestinal epithelial cells ($f_{u\ gut}$) was set as 1 (default). The contribution ratio to overall elimination (fraction metabolized [fm]) was set as 0.35 for CYP3A4 and 0.04 for CYP1A2 based on the *in vitro* metabolism study [see Section 4.3.1] and the mass balance study. The renal clearance (CL_r of maribavir) was set as 0.051 L/h based on the foreign phase I study (Study CAMB1001) [see Section 6.2.1.1]. The inhibition constants K_i (μmol/L) used for transporters were 33.8 or 1.2 for P-gp, 0.23 or 0.062 for BCRP, 3.03 for OATP1B1, and 3.29 for OATP1B3, as estimated based on the *in vitro* inhibition study [see Section 4.5.4] or using the Simcyp In Vitro Analysis tool kit.
The model was built using the results of maribavir monotherapy in the foreign phase I study (Study CAMB1001) and the drug interaction study with rifampicin (Study 1263-110) [see Section 6.2.4]. The model was verified for the concomitant use of maribavir with P-gp substrates based on the results of the drug interaction study with digoxin (Study SHP620-115) [see Section 6.2.4].

precautions in the package insert regarding concomitant use of maribavir with the BCRP substrate drugs is understandable. However, the PBPK model used for the prediction has not been validated (validation, etc. using the data observed in the clinical drug interaction studies of maribavir with BCRP substrate drugs) to confirm that the model can appropriately predict drug interactions between maribavir and BCRP substrates. Information on the concomitant use of maribavir with BCRP substrate drugs should therefore be continuously collected, including the published literature, and new findings should be provided to healthcare professionals immediately when they become available.

Concerning MATE1 and UGT1A1, on which maribavir showed an inhibitory effect in *in vitro* studies [see Sections 4.5.1 and 4.5.4], no definitive information requiring the provision of precautions regarding the concomitant use of maribavir with MATE1 or UGT1A1 substrate drugs has been obtained to date. However, since no clinical drug interaction studies on the concomitant use of maribavir with MATE1 or UGT1A1 substrate drugs have been conducted, information should be continuously collected, even in the post-marketing setting, and new findings should be provided to healthcare professionals immediately when they become available.

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

The applicant submitted main efficacy and safety data, in the form of the clinical study results shown in Table 37.

Table 37. Summary of main clinical studies

Data category	Region	Study	Phase	Population	No. of enrolled subjects	Outline of dosage regimen	Main endpoints [Primary endpoint]
Evaluation	Foreign	202	II	HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance)	120	Maribavir 400, 800, or 1,200 mg BID, p.o, for up to 24 weeks.	Safety Efficacy PK
Evaluation	Foreign	303	III	HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance)	[1] 235 [2] 117	[1] Maribavir group Maribavir 400 mg BID, p.o., for 8 weeks. [2] IAT group One or 2 drugs of GCV i.v., VGCV p.o., FOS i.v., or cidofovir i.v., for 8 weeks. For part of subjects assigned to the IAT group, maribavir 400 mg BID, p.o., for 8 weeks, as rescue therapy.	Efficacy [the proportion of subjects achieving confirmed CMV viremia clearance at the end of Week 8] Safety PK
Evaluation	Japanese	3001	III	HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance) or asymptomatic CMV viremia	41	Maribavir 400 mg BID, p.o., for 8 weeks.	Efficacy [the proportion of subjects achieving confirmed CMV viremia clearance at the end of Week 8] Safety PK

7.1 Phase II studies

7.1.1 Foreign phase II study (CTD 5.3.5.2-1: Study 202 [July 2012 to December 2014])

A randomized, double-blind, parallel-group study was conducted in the US to investigate the safety, efficacy, and PK of maribavir in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance) (target sample size, 120 subjects [40 in each group]). Table 38 shows the main inclusion/exclusion criteria in this study.

Table 38. Main inclusion/exclusion criteria

Inclusion criteria	1. Patients aged ≥12 years. 2. HSCT or SOT recipients. 3. Patients with CMV infection detected in blood or plasma, with the value at screening ≥1,000 copies/mL, as determined by quantitative polymerase chain reaction (qPCR) or an equivalent quantitative CMV measurement method at the central laboratory or the study site. 4. Patients with current CMV disease refractory[a)] or resistant[b)] to GCV, VGCV, or FOS.
Exclusion criteria	1. Patients on treatment with GCV, VGCV, FOS, cidofovir, CMV immunoglobulin, leflunomide, artesunate, or an investigational product (unapproved) with anti-CMV activity at the start of the study treatment. 2. Patients recognized by the investigator to have refractory or resistant CMV disease due to inadequate adherence to CMV treatment in the past. 3. Patients with severe (Child-Pugh C) hepatic impairment at screening. 4. Patients requiring mechanical ventilation or a vasopressor for hemodynamic support at enrollment.

a) Defined as documented failure to achieve >1 $\log_{10}$ decrease in blood or plasma CMV DNA level after ≥2 weeks of treatment with intravenous GCV, oral VGCV, or intravenous FOS (or a combination of them).
b) Defined as documented failure to achieve >1 $\log_{10}$ decrease in blood or plasma CMV DNA level after ≥2 weeks of treatment with intravenous GCV, oral VGCV, or intravenous FOS (or a combination of them), AND documentation of 1 or more CMV gene mutations related to resistance to GCV, VGCV, or FOS.

Maribavir (400 mg, 800 mg, or 1,200 mg) was orally administered twice daily. Only subjects who achieved a virologic response[38)] at the Week 3 and Week 6 visits continued the study treatment after Week 3 and Week 6, respectively, at the discretion of the investigator. They were allowed to continue the treatment for up to 24 weeks.

All 120 randomized subjects (40 subjects in the maribavir 400 mg group, 40 subjects in the maribavir 800 mg group, and 40 subjects in the maribavir 1,200 mg group) received ≥1 dose of the study drug and were included in the ITT-S analysis population and the safety analysis population. The ITT-S analysis population was used as the efficacy analysis population.

Study treatment was discontinued in 37.5% (15 of 40) of subjects in the maribavir 400 mg BID group, 37.5% (15 of 40) of subjects in the maribavir 800 mg BID group, and 40.0% (16 of 40) of subjects in the maribavir 1,200 mg BID group. The reasons for treatment discontinuation were death (10 subjects in the maribavir 400 mg BID group, 12 subjects in the maribavir 800 mg BID group, and 10 subjects in the maribavir 1,200 mg BID group), investigator's decision (5 subjects in the maribavir 400 mg BID group, 1 subject in the maribavir 800 mg BID group, and 2 subjects in the maribavir 1,200 mg BID group), subject's request (1 subject in the maribavir 800 mg BID group and 4 subjects in the maribavir 1,200 mg BID group), and lost to follow up (1 subject in the maribavir 800 mg BID group).

38) Virologic response was determined as follows:
Week 3 visit: Subjects with any decline in CMV DNA level from baseline at Week 2.
Week 6 visit: Subjects with ≥2 $\log_{10}$ decline in CMV DNA level from baseline at Week 5 or CMV DNA level below the LLOQ.

Concerning the safety, the incidence of adverse events and adverse drug reactions observed by 7 days after the last dose of the study drug was 100% (40 of 40 subjects) and 77.5% (31 of 40 subjects), respectively, in the maribavir 400 mg BID group, 100% (40 of 40 subjects) and 80.0% (32 of 40 subjects), respectively, in the maribavir 800 mg BID group, and 100% (40 of 40 subjects) and 75.0% (30 of 40 subjects), respectively, in the maribavir 1,200 mg group. Table 39 shows the adverse events and adverse drug reactions observed in ≥7.5% of subjects in the overall maribavir group.

Table 39. Adverse events and adverse drug reactions with incidence of ≥7.5% in the overall maribavir group (safety analysis population)

Event	Adverse events			Adverse drug reactions		
	Maribavir 400 mg BID (N = 40)	Maribavir 800 mg BID (N = 40)	Maribavir 1,200 mg BID (N = 40)	Maribavir 400 mg BID (N = 40)	Maribavir 800 mg BID (N = 40)	Maribavir 1,200 mg BID (N = 40)
Overall	40 (100)	40 (100)	40 (100)	31 (77.5)	32 (80.0)	30 (75.0)
Dysgeusia	24 (60.0)	25 (62.5)	29 (72.5)	24 (60.0)	25 (62.5)	29 (72.5)
Nausea	15 (37.5)	12 (30.0)	14 (35.0)	7 (17.5)	8 (20.0)	10 (25.0)
Vomiting	11 (27.5)	13 (32.5)	11 (27.5)	1 (2.5)	2 (5.0)	5 (12.5)
Oedema peripheral	11 (27.5)	6 (15.0)	6 (15.0)	0	0	0
Headache	9 (22.5)	4 (10.0)	6 (15.0)	0	1 (2.5)	3 (7.5)
Fatigue	8 (20.0)	10 (25.0)	7 (17.5)	1 (2.5)	1 (2.5)	2 (5.0)
Anaemia	7 (17.5)	7 (17.5)	10 (25.0)	3 (7.5)	2 (5.0)	2 (5.0)
Rash	7 (17.5)	6 (15.0)	3 (7.5)	3 (7.5)	2 (5.0)	3 (7.5)
Cytomegalovirus infection	6 (15.0)	12 (30.0)	10 (25.0)	2 (5.0)	7 (17.5)	2 (5.0)
Pneumonia	6 (15.0)	4 (10.0)	5 (12.5)	0	0	0
Urinary tract infection	6 (15.0)	3 (7.5)	3 (7.5)	0	0	0
Pyrexia	6 (15.0)	6 (15.0)	3 (7.5)	0	0	0
Diarrhoea	5 (12.5)	13 (32.5)	10 (25.0)	0	3 (7.5)	6 (15.0)
Cough	5 (12.5)	6 (15.0)	2 (5.0)	0	0	0
Constipation	5 (12.5)	5 (12.5)	5 (12.5)	1 (2.5)	0	0
Hypotension	5 (12.5)	5 (12.5)	1 (2.5)	0	0	0
Dehydration	5 (12.5)	4 (10.0)	3 (7.5)	0	0	0
Pruritus	5 (12.5)	1 (2.5)	5 (12.5)	3 (7.5)	0	3 (7.5)
Immunosuppressant drug level increased	4 (10.0)	2 (5.0)	6 (15.0)	3 (7.5)	2 (5.0)	6 (15.0)
Dyspnoea	4 (10.0)	2 (5.0)	5 (12.5)	0	1 (2.5)	0
Clostridium difficile infection	4 (10.0)	2 (5.0)	4 (10.0)	0	0	0
Back pain	4 (10.0)	1 (2.5)	4 (10.0)	0	0	0
Renal impairment	3 (7.5)	7 (17.5)	9 (22.5)	1 (2.5)	0	2 (5.0)
Decreased appetite	3 (7.5)	5 (12.5)	4 (10.0)	1 (2.5)	2 (5.0)	2 (5.0)
Abdominal pain	3 (7.5)	4 (10.0)	3 (7.5)	0	0	0
Depression	2 (5.0)	8 (20.0)	1 (2.5)	0	0	0
Hypokalaemia	2 (5.0)	4 (10.0)	6 (15.0)	0	1 (2.5)	0
Acute graft versus host disease	2 (5.0)	4 (10.0)	3 (7.5)	0	0	0
Hyperkalaemia	2 (5.0)	3 (7.5)	5 (12.5)	0	0	0
Weight decreased	2 (5.0)	3 (7.5)	4 (10.0)	0	0	2 (5.0)
Dizziness	1 (2.5)	5 (12.5)	3 (7.5)	0	2 (5.0)	0

n (%). Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.

Adverse events leading to death occurred in 25.0% (10 of 40) of subjects in the maribavir 400 mg BID group, 30.0% (12 of 40) of subjects in the maribavir 800 mg BID group, and 25.0% (10 of 40) of subjects in the maribavir 1,200 mg BID group. Table 40 shows the breakdown of these adverse events. A causal relationship with the study drug was not ruled out in 1 subject in the maribavir 800 mg BID group (multi-organ failure).

Table 40. Breakdown of adverse events leading to death (safety analysis population)

Maribavir 400 mg BID	Sepsis in 2 subjects, and cardio-respiratory arrest, multi-organ failure, cytomegalovirus infection, leukaemia recurrent, oesophageal carcinoma, central nervous system haemorrhage, encephalopathy, renal dysfunction, and acute respiratory distress syndrome in 1 subject each (some subjects developed >1 event).
Maribavir 800 mg BID	Pneumonia in 2 subjects, and multi-organ failure, acute graft versus host disease, bacteraemia, encephalitis cytomegalovirus, herpes simplex meningoencephalitis, sepsis, myelodysplastic syndrome, post transplant lymphoproliferative disorder, cerebral haemorrhage, and renal dysfunction in 1 subject each.
Maribavir 1,200 mg	Multi-organ failure, sepsis, pneumonia cytomegaloviral, and renal dysfunction in 2 subjects each, and acute graft versus host disease, nocardiosis, leukaemia recurrent, acute respiratory distress syndrome, and respiratory failure in 1 subject each (some subjects developed >1 event).

Serious adverse events occurred in 70.0% (28 of 40) of subjects in the maribavir 400 mg BID group, 67.5% (27 of 40) of subjects in the maribavir 800 mg BID group, and 65.0% (26 of 40) of subjects in the maribavir 1,200 mg BID group. Table 41 shows the breakdown of these adverse events. Among them, a causal relationship of any of the adverse events to the study drug was not ruled out in 8 subjects in the maribavir 400 mg BID group (cytomegalovirus infection and anaemia in 2 subjects each, and nausea, acute prerenal failure, blood stem cell transplant failure, fatigue, pneumonia cytomegaloviral, renal dysfunction, and vision blurred in 1 subject each [some subjects developed >1 event]), 7 subjects in the maribavir 800 mg BID group (cytomegalovirus infection in 3 subjects, nausea in 2 subjects, and diarrhoea, dyspnoea exertional, encephalopathy, multi-organ failure, and vomiting in 1 subject each [some subjects developed >1 event]), and 5 subjects in the maribavir 1,200 mg BID group (nausea in 2 subjects, and failure to thrive, immunosuppressant drug level increased, and orthostatic hypotension in 1 subject each). All of these events resolved or were resolving, except for events that did not resolve in 2 subjects in the maribavir 400 mg BID group (blood stem cell transplant failure and vision blurred in 1 subject each) and 2 subjects in the 800 mg BID group (encephalopathy and cytomegalovirus infection in 1 subject each).

Table 41. Breakdown of serious adverse events (safety analysis population)

Maribavir 400 mg BID	Anaemia in 4 subjects, cytomegalovirus infection in 3 subjects, renal dysfunction, sepsis, lung transplant rejection, clostridium difficile infection, leukaemia recurrent, pyrexia, and cytomegalovirus gastroenteritis in 2 subjects each, and nausea, dehydration, multi-organ failure, pneumonia, bacteraemia, failure to thrive, pneumonia cytomegaloviral, acute graft versus host disease, encephalopathy, Escherichia bacteraemia, abdominal pain, acute prerenal failure, adenovirus infection, appendicitis, ascites, bacterial sepsis, bile duct stenosis, blood stem cell transplant failure, bronchiolitis, cardiac tamponade, central nervous system haemorrhage, chronic obstructive pulmonary disease, encephalitis viral, fatigue, focal segmental glomerulosclerosis, gout, haematemesis, haemolysis, hyponatraemia, hypotension, jugular vein thrombosis, mental status changes, pericardial effusion, small intestinal obstruction, vision blurred, and oesophageal carcinoma in 1 subject each (some subjects developed >1 event).
Maribavir 800 mg BID	Cytomegalovirus infection in 5 subjects, nausea, renal dysfunction, and sepsis in 3 subjects each, pneumonia, bacteraemia, and diarrhoea in 2 subjects each, and dehydration, lung transplant rejection, multi-organ failure, failure to thrive, pyrexia, encephalopathy, pancreatitis, urinary tract infection, asthenia, cardiac failure congestive, cholecystitis, cytomegalovirus chorioretinitis, dyspnoea exertional, encephalitis cytomegalovirus, fall, fluid overload, gastrointestinal haemorrhage, generalised oedema, herpes simplex meningoencephalitis, ileus, Klebsiella bacteraemia, oedema peripheral, pancytopenia, parvovirus infection, post transplant lymphoproliferative disorder, spondylitic myelopathy, and vomiting in 1 subject each (some subjects developed >1 event).
Maribavir 1,200 mg BID	Cytomegalovirus infection in 6 subjects, nausea and respiratory failure in 3 subjects each, renal dysfunction, dehydration, multi-organ failure, pneumonia cytomegaloviral, and acute respiratory distress syndrome in 2 subjects each, and sepsis, lung transplant rejection, pneumonia, clostridium difficile infection, diarrhoea, failure to thrive, leukaemia recurrent, acute graft versus host disease, Escherichia bacteraemia, pancreatitis, urinary tract infection, arteriovenous fistula site infection, catheter site infection, cellulitis, convulsion, diffuse alveolar damage, hyperglycaemia, hyperkalaemia, hypokalaemia, jejunal ulcer, nocardiosis, orthostatic hypotension, oxygen saturation decreased, pneumocystis jirovecii pneumonia, respiratory syncytial virus infection, rhinovirus infection, and immunosuppressant drug level increased in 1 subject each (some subjects developed >1 event).

Adverse events leading to treatment discontinuation occurred in 27.5% (11 of 40) of subjects in the maribavir 400 mg BID group, 42.5% (17 of 40) of subjects in the maribavir 800 mg BID group, and 32.5% (13 of 40) of

subjects in the maribavir 1,200 mg BID group. Table 42 shows the breakdown of these adverse events. Among them, a causal relationship of any of the adverse event to the study drug was not ruled out in 3 subjects in the maribavir 400 mg BID group (cytomegalovirus infection, nausea, and pneumonia cytomegaloviral in 1 subject each), 8 subjects in the maribavir 800 mg BID group (cytomegalovirus infection in 5 subjects, and nausea, blood creatinine increased, diarrhoea, encephalopathy, and vomiting in 1 subject each [some subjects developed >1 event]), and 4 subjects in the maribavir 1,200 mg BID group (nausea, anaemia, dysgeusia, and immunosuppressant drug level increased in 1 subject each). All of these events resolved or were resolving, except for events that did not resolve in 3 subjects in the maribavir 800 mg BID group (encephalopathy, blood creatinine increased, and cytomegalovirus infection in 1 subject each) and an event that resolved with sequelae in 1 subject in the maribavir 800 mg BID group (cytomegalovirus infection).

Table 42. Breakdown of adverse events leading to treatment discontinuation (safety analysis population)

Maribavir 400 mg BID	Cytomegalovirus infection in 4 subjects, and nausea, encephalopathy, multi-organ failure, renal dysfunction, cytomegalovirus gastroenteritis, pneumonia cytomegaloviral, and sepsis in 1 subject each.
Maribavir 800 mg BID	Cytomegalovirus infection in 8 subjects, and nausea, encephalopathy, renal dysfunction, bacteraemia, blood creatinine increased, cytomegalovirus chorioretinitis, diarrhoea, dysphagia, encephalitis cytomegalovirus, post transplant lymphoproliferative disorder, and vomiting in 1 subject each (some subjects developed >1 event).
Maribavir 1,200 mg BID	Cytomegalovirus infection in 5 subjects, and nausea, multi-organ failure, anaemia, clonus, dysgeusia, immunosuppressant drug level increased, liver transplant rejection, and Pneumocystis jirovecii pneumonia in 1 subject each.

According to the efficacy analysis, the proportion of subjects achieving confirmed CMV viremia clearance[39)] within 6 weeks of treatment in the ITT-S analysis population, which was assessed as the primary endpoint, was 70.0% (28 of 40 subjects) in the maribavir 400 mg BID group, 62.5% (25 of 40 subjects) in the maribavir 800 mg BID group, and 67.5% (27 of 40 subjects) in the maribavir 1,200 mg BID group.

7.2 Phase III studies

7.2.1 Foreign phase III study (CTD 5.3.5.1-3: Study 303 [December 2016 to August 2020])

A randomized, open-label, active-controlled study was conducted in 12 countries or regions, including the US, France, and Belgium, to investigate the efficacy, safety, and PK of maribavir in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance) (target sample size, approximately 351 subjects [234 subjects in the maribavir group and 117 subjects in the investigator-assigned anti-CMV treatment (IAT) group][40)]). Table 43 shows the main inclusion/exclusion criteria in this study.

[39)] Defined as a condition in which plasma CMV DNA levels were below the LLOQ (200 copies/mL) for post-baseline samples, in 2 consecutive assessments separated by ≥5 days (at the central laboratory).

[40)] Assuming that the proportion of subjects achieving confirmed CMV viremia clearance at the end of Week 8, which was assessed as the primary endpoint, would be 60% in the maribavir group and 40% in the IAT group, and taking into account the randomization ratio of 2:1 and the number of subjects required to provide a power of 90% under a two-sided significance level of 5% with a dropout rate of 10%, the target sample size was set as 351 subjects (234 subjects in the maribavir group and 117 subjects in the IAT group).

Table 43. Main inclusion/exclusion criteria

Inclusion criteria	1. Patients aged ≥12 years. 2. HSCT or SOT recipients. 3. Patients with CMV infection (CMV DNA level at screening ≥2,730 IU/mL in whole blood or ≥910 IU/mL in plasma in 2 consecutive assessments[a)] performed at an interval of ≥1 day) confirmed based on the results of qPCR or an equivalent quantitative CMV DNA test at the study site or the central laboratory. 4. Patients with current CMV disease refractory[b)] to the recently administered 4 anti-CMV drugs. Patients confirmed to have ≥1 CMV gene mutation related to resistance to GCV, VGCV, FOS, or cidofovir must also meet the definition of refractory CMV disease.
Exclusion criteria	1. Patients recognized by the investigator to have refractory or resistant CMV disease due to inadequate adherence to CMV treatment in the past. 2. Patients requiring treatment with GCV, VGCV, FOS, or cidofovir for disease other than CMV disease at the start of the study treatment or those considered to require concomitant use of these drugs in addition to maribavir for CMV infection. 3. Patients on treatment with leflunomide, letermovir, or artesunate at the start of the study treatment. 4. Patients with tissue-invasive CMV disease in the central nervous system (including the retina). 5. Patients requiring mechanical ventilation or a vasopressor for hemodynamic support at enrollment. 6. Patients receiving treatment for acute or chronic hepatitis C.

a) Both specimens were collected within 14 days (1 of them was collected within 5 days) before the first dose of the study drug. The 2 tests were performed using the same sample type (whole blood or plasma) at the same laboratory.
b) Defined as documented failure to achieve >1 $\log_{10}$ decrease in blood or plasma CMV DNA level after ≥14 days of treatment with intravenous GCV, oral VGCV, intravenous FOS, or intravenous cidofovir.

Maribavir 400 mg was orally administered twice daily in the maribavir group, and 1 or 2 drugs selected by the investigator from intravenous GCV/oral valganciclovir (VGCV), intravenous FOS, and intravenous cidofovir for each subject were administered in the IAT group. The treatment period was 8 weeks. In the IAT group, subjects in whom the virologic treatment was found to have failed (regardless of intolerance) after ≥3 weeks of IAT treatment were allowed to enter the rescue group after 3 weeks of the study treatment (from the visit after the 3-week treatment) in the judgment of the medical monitor. In the rescue group, maribavir 400 mg was orally administered twice daily, and the treatment period was 8 weeks.

A total of 352 randomized[41)] subjects (235 subjects in the maribavir group and 117 subjects in the IAT group) were included in the randomization population and also in the efficacy analysis population. Of the randomized population, 350 subjects who received ≥1 dose of the study drug (234 subjects in the maribavir group and 116 subjects in the IAT group[42)]) were included in the safety analysis population. The rescue group consisted of 22 subjects.

Study treatment was discontinued 15.3% (36 of 235) of subjects in the maribavir group and 31.6% (37 of 117) of subjects in the IAT group. The main reasons for treatment discontinuation were death (24 subjects in the maribavir group and 8 subjects in the IAT group), consent withdrawal (8 subjects in the maribavir group and 16 subjects in the IAT group), and non-compliance with study procedures, visits, or treatment (0 subjects in the maribavir group and 6 subjects in the IAT group). In the rescue group, study treatment was discontinued in 9.1% (2 of 22) of subjects, and the reasons for treatment discontinuation were sponsor's decision (1 subject) and transfer to another hospital (1 subject).

41) The subjects were randomized in a 2:1 ratio to maribavir or IAT based on the stratification factors of transplantation type (HSCT and SOT) and the most recent CMV DNA level (high, intermediate, and low) at screening.
42) The IAT group consisted of 28 subjects treated with GCV, 28 subjects treated with VGCV, 47 subjects treated with FOS, 6 subjects treated with cidofovir, 4 subjects treated with FOS and VGCV, and 3 subjects treated with FOS and GCV.

Concerning the efficacy, the proportion of subjects achieving confirmed CMV viremia clearance[43] at Week 8, which was assessed as the primary endpoint, was 55.7% (131 of 235 subjects) in the maribavir group and 23.9% (28 of 117 subjects) in the IAT group. The intergroup difference [95% CI] (*P* value[44]) was 31.8 [21.81, 41.82] (<0.001), showing a statistically significant difference.

Concerning the safety, the incidence of adverse events and adverse drug reactions observed in the on-treatment observation period (until 7 days after the last dose of the study drug) was 97.4% (228 of 234 subjects) and 60.3% (141 of 234 subjects), respectively, in the maribavir group, and 91.4% (106 of 116 subjects) and 49.1% (57 of 116 subjects), respectively, in the IAT group. Table 44 shows the adverse events and adverse drug reactions observed in ≥5% of subjects in the maribavir group or the IAT group.

Table 44. Adverse events and adverse drug reactions with incidence of ≥5% in the maribavir group or the IAT group (on-treatment observation period; safety analysis population and rescue group[a])

Event	Adverse events			Adverse drug reactions		
	Maribavir (N = 234)	IAT (N = 116)	Rescue therapy (N = 22)	Maribavir (N = 234)	IAT (N = 116)	Rescue therapy (N = 22)
Overall	228 (97.4)	106 (91.4)	22 (100)	141 (60.3)	57 (49.1)	13 (59.1)
Dysgeusia	87 (37.2)	4 (3.4)	8 (36.4)	84 (35.9)	1 (0.9)	8 (36.4)
Nausea	50 (21.4)	25 (21.6)	6 (27.3)	20 (8.5)	11 (9.5)	0
Diarrhoea	44 (18.8)	24 (20.7)	8 (36.4)	9 (3.8)	6 (5.2)	2 (9.1)
Vomiting	33 (14.1)	19 (16.4)	5 (22.7)	18 (7.7)	5 (4.3)	0
Anaemia	29 (12.4)	14 (12.1)	3 (13.6)	3 (1.3)	9 (7.8)	0
Fatigue	28 (12.0)	10 (8.6)	2 (9.1)	2 (0.9)	1 (0.9)	0
Pyrexia	24 (10.3)	17 (14.7)	2 (9.1)	1 (0.4)	1 (0.9)	0
Cytomegalovirus viraemia	24 (10.3)	6 (5.2)	2 (9.1)	9 (3.8)	1 (0.9)	1 (4.5)
Neutropenia	22 (9.4)	26 (22.4)	0	4 (1.7)	16 (13.8)	0
Immunosuppressant drug level increased	21 (9.0)	1 (0.9)	1 (4.5)	14 (6.0)	0	0
Taste disorder	21 (9.0)	1 (0.9)	2 (9.1)	20 (8.5)	1 (0.9)	2 (9.1)
Acute kidney injury	20 (8.5)	11 (9.5)	3 (13.6)	4 (1.7)	9 (7.8)	0
Headache	19 (8.1)	15 (12.9)	2 (9.1)	2 (0.9)	4 (3.4)	0
Abdominal pain	18 (7.7)	3 (2.6)	2 (9.1)	5 (2.1)	0	0
Decreased appetite	18 (7.7)	9 (7.8)	1 (4.5)	3 (1.3)	3 (2.6)	0
Dizziness	17 (7.3)	5 (4.3)	0	2 (0.9)	1 (0.9)	0
Oedema peripheral	17 (7.3)	9 (7.8)	3 (13.6)	0	4 (3.4)	0
Blood creatinine increased	13 (5.6)	5 (4.3)	0	1 (0.4)	3 (2.6)	1 (4.5)
Dyspnoea	13 (5.6)	8 (6.9)	1 (4.5)	0	1 (0.9)	0
Arthralgia	13 (5.6)	3 (2.6)	1 (4.5)	1 (0.4)	1 (0.9)	0
Cough	13 (5.6)	7 (6.0)	5 (22.7)	0	1 (0.9)	0
Cytomegalovirus infection reactivation	12 (5.1)	3 (2.6)	0	0	1 (0.9)	0
Thrombocytopenia	11 (4.7)	7 (6.0)	1 (4.5)	0	6 (5.2)	0
Hypomagnesaemia	9 (3.8)	10 (8.6)	2 (9.1)	0	5 (4.3)	0
Constipation	9 (3.8)	7 (6.0)	2 (9.1)	0	0	0
Hypertension	9 (3.8)	8 (6.9)	2 (9.1)	0	0	0
Hypokalaemia	8 (3.4)	11 (9.5)	4 (18.1)	1 (0.4)	5 (4.3)	0
Abdominal pain upper	8 (3.4)	6 (5.2)	0	2 (0.9)	0	0
Leukopenia	7 (3.0)	8 (6.9)	2 (9.1)	0	5 (4.3)	0
Pain in extremity	5 (2.1)	6 (5.2)	2 (9.1)	0	0	0

n (%). MedDRA version 23.0.

a) The adverse events in the rescue group are those that occurred in the observation period on treatment with rescue therapy (from the start of rescue therapy until 7 days after the last dose of rescue therapy or the start of alternative anti-GMV treatment, whichever came earlier).

[43] Defined as a condition in which plasma CMV DNA levels were below the LLOQ (137 IU/mL) for post-baseline samples, in 2 consecutive assessments separated by ≥5 days (at the central laboratory).

[44] Cochran-Mantel-Haenszel test with transplantation type and plasma CMV DNA level at baseline as stratification factors, with a two-sided significance level of 0.05.

Adverse events leading to death occurred in 6.8% (16 of 234) of subjects in the maribavir group, 5.2% (6 of 116 subjects) in the IAT group, and 4.5% (1 of 22 subjects) in the rescue group. Table 45 shows the breakdown of these adverse events. A causal relationship of any of the adverse events to the study drug was not ruled out in 1 subject in the maribavir group (drug interaction) and 1 subject in the IAT group (febrile neutropenia).

Table 45. Breakdown of adverse events leading to death (on-treatment observation period)

Maribavir	Respiratory failure in 2 subjects, and acute graft versus host disease, leukaemia recurrent, hypoxia, cardiac arrest, acute lymphocytic leukaemia recurrent, deep vein thrombosis, multiple organ dysfunction syndrome, cytomegalovirus colitis, drug interaction, cytomegalovirus syndrome, dyspnoea, general physical health deterioration, pulmonary embolism, acute myeloid leukaemia recurrent, and septic shock in 1 subject each (some subjects developed >1 event).
IAT	Leukaemia recurrent, encephalitis cytomegalovirus, respiratory failure, acute respiratory distress syndrome, febrile neutropenia, pneumonia, tuberculosis, and acute myeloid leukaemia recurrent in 1 subject each (some subjects developed >1 event).
Rescue therapy	Encephalitis cytomegalovirus in 1 subject.

Serious adverse events occurred in 38.5% (90 of 234) of subjects in the maribavir group, 37.1% (43 of 116) of subjects in the IAT group, and 50% (11 of 22) of subjects in the rescue group. Table 46 shows the breakdown of these adverse events. Among them, a causal relationship of any of the adverse events to the study drug was not ruled out in 12 subjects in the maribavir group (acute kidney injury in 3 subjects, cytomegalovirus viraemia in 2 subjects, and nausea, vomiting, drug interaction, pyrexia, treatment failure, hepatic failure, cytomegalovirus infection, cytomegalovirus syndrome, gastroenteritis, hepatic enzyme increased, and immunosuppressant drug level increased in 1 subject each [some subjects developed >1 event]), 17 subjects in the IAT group (febrile neutropenia and acute kidney injury in 4 subjects each, neutropenia, nausea, and vomiting in 2 subjects each, and pyrexia, encephalitis viral, general physical condition abnormal, hypokalaemia, and renal dysfunction in 1 subject each [some subjects developed >1 event]), and 1 subject in the rescue group (cytomegalovirus viraemia in 1 subject). All of these events resolved, except for the events that did not resolve or resulted in death in 4 subjects in the maribavir group (cytomegalovirus viraemia, hepatic failure, drug interaction, and treatment failure in 1 subject each) and 2 subjects in the IAT group (febrile neutropenia and general physical condition abnormal in 1 subject each).

Table 46. Breakdown of serious adverse events (on-treatment observation period)

Maribavir	Acute kidney injury in 8 subjects, cytomegalovirus viraemia in 7 subjects, cytomegalovirus infection in 6 subjects, diarrhoea in 4 subjects, anaemia, abdominal pain, gastrointestinal haemorrhage, pyrexia, encephalitis cytomegalovirus, and respiratory failure in 3 subjects each, febrile neutropenia, thrombocytopenia, nausea, general physical health deterioration, bacteraemia, cytomegalovirus chorioretinitis, cytomegalovirus infection reactivation, cytomegalovirus syndrome, Escherichia sepsis, herpes zoster, pneumonia, pneumonia cytomegaloviral, septic shock, staphylococcal bacteraemia, failure to thrive, mental status changes, dyspnoea, hypoxia, graft versus host disease in gastrointestinal tract, and deep vein thrombosis in 2 subjects each, and leukocytosis, pancytopenia, sickle cell anaemia with crisis, thrombotic microangiopathy, acute myocardial infarction, cardiac arrest, pericarditis, tachycardia, pancreatitis, vomiting, adverse drug reaction, asthenia, drug interaction, fatigue, malaise, multiple organ dysfunction syndrome, treatment failure, drug-induced liver injury, hepatic failure, acute graft versus host disease, graft versus host diseae in liver, transplant rejection, arthritis bacterial, Aspergillus infection, bronchopulmonary aspergillosis, cytomegalovirus colitis, cytomegalovirus mucocutaneous ulcer, device related infection, device related sepsis, enterococcal bacteraemia, erysipelas, Escherichia bacteraemia, gastroenteritis, gastroenteritis rotavirus, H1N1 influenza, herpes zoster meningoencephalitis, infection, influenza, osteomyelitis, pneumonia cryptococcal, pneumonia haemophilus, pseudomonal sepsis, pulmonary tuberculosis, respiratory tract infection, varicella zoster virus infection, viral upper respiratory tract infection, procedural pneumothorax, transplant dysfunction, haemoglobin decreased, hepatic enzyme increased, immunosuppressant drug level increased, viral load increased, dehydration, hyponatraemia, back pain, acute lymphocytic leukaemia recurrent, acute myeloid leukaemia recurrent, leukaemia recurrent, renal cell carcinoma, haematuria, pleural effusion, pneumomediastinum, pneumothorax, pulmonary embolism, pulmonary mass, respiratory distress, and orthostatic hypotension in 1 subject each (some subjects developed >1 event).
IAT	Febrile neutropenia, cytomegalovirus infection, and acute kidney injury in 4 subjects each, neutropenia and cytomegalovirus viraemia in 3 subjects each, nausea, vomiting, pyrexia, leukaemia recurrent, and hypokalaemia in 2 subjects each, and cardiac failure congestive, colitis, gastrointestinal haemorrhage, haematochezia, disease progression, cholecystitis, BK virus infection, bacteraemia, bacterial pyelonephritis, cytomegalovirus chorioretinitis, encephalitis cytomegalovirus, encephalitis viral, herpes simplex, periorbital cellulitis, pneumonia, pneumonia cytomegaloviral, respiratory syncytial virus infection, sinusitis, streptococcal bacteraemia, incorrect dose administered, spinal fracture, general physical condition abnormal, acute myeloid leukaemia recurrent, paraesthesia, substance-induced psychotic disorder, nephrolithiasis, renal dysfunction, acute respiratory distress syndrome, acute respiratory failure, dyspnoea, hypoxia, respiratory failure, and hypertension in 1 subject each (some subjects developed >1 event).
Rescue therapy	Anaemia in 2 subjects, and cytomegalovirus colitis, cytomegalovirus infection, cytomegalovirus viraemia, encephalitis cytomegalovirus, herpes zoster, pyelonephritis, respiratory tract infection, vascular device infection, spinal fracture, acute kidney injury, vesicoureteric reflux, cough, and deep vein thrombosis in 1 subject each (some subjects developed >1 event).

Adverse events leading to treatment discontinuation occurred in 13.2% (31 of 234) of subjects in the maribavir group, 31.9% (37 of 116) of subjects in the IAT group, and 4.5% (1 of 22) of subjects in the rescue group. Table 47 shows the breakdown of these adverse events. Among them, a causal relationship of any of the adverse events to the study drug was not ruled out in 11 subjects in the maribavir group (diarrhoea, nausea, cytomegalovirus infection, and dysgeusia in 2 subjects each, and vomiting, pyrexia, hepatic failure, hyperbilirubinaemia, cytomegalovirus syndrome, cytomegalovirus viraemia, hepatic enzyme increased, arthralgia, and headache in 1 subject each [some subjects developed >1 event]), 27 subjects in the IAT group (neutropenia in 11 subjects, acute kidney injury in 6 subjects, thrombocytopenia in 4 subjects, leukopenia in 3 subjects, anaemia and renal dysfunction in 2 subjects each, and diarrhoea, nausea, vomiting, oedema peripheral, cytomegalovirus viraemia, encephalitis viral, blood creatinine increased, weight decreased, white blood cell count decreased, delirium, nephropathy toxic, proteinuria, and renal failure in 1 subject each [some subjects developed >1 event]), and 1 subject in the rescue group (blood creatinine increased in 1 subject). All of these events resolved, except for the events that did not resolve in 2 subjects in the maribavir group (cytomegalovirus viraemia, hyperbilirubinaemia, and hepatic failure in 1 subject each [1 subject developed >1 event]) and 6 subjects in the IAT group (acute kidney injury, thrombocytopenia, cytomegalovirus viraemia, blood creatinine increased, renal dysfunction, weight decreased, proteinuria, and renal failure in 1 subject each [some subjects developed >1 event]).

Table 47. Breakdown of adverse events leading to treatment discontinuation (on-treatment observation period)

Maribavir	Cytomegalovirus infection in 7 subjects, cytomegalovirus viraemia in 4 subjects, diarrhoea, nausea, cytomegalovirus infection reactivation, encephalitis cytomegalovirus, acute lymphocytic leukaemia recurrent, and dysgeusia in 2 subjects each, and vomiting, general physical health deterioration, pyrexia, hepatic failure, hyperbilirubinaemia, cytomegalovirus syndrome, pulmonary tuberculosis, septic shock, hepatic enzyme increased, arthralgia, headache, mental status changes, hypoxia, pneumomediastinum, pulmonary embolism, and respiratory failure in 1 subject each (some subjects developed >1 event).
IAT	Neutropenia in 11 subjects, acute kidney injury in 6 subjects, thrombocytopenia in 4 subjects, leukopenia in 3 subjects, anaemia, cytomegalovirus viraemia, renal failure, and renal dysfunction in 2 subjects each, and diarrhoea, nausea, vomiting, oedema peripheral, BK virus infection, cytomegalovirus chorioretinitis, cytomegalovirus infection, encephalitis cytomegalovirus, encephalitis viral, viral haemorrhagic cystitis, blood creatinine increased, weight decreased, white blood cell count decreased, acute myeloid leukaemia recurrent, leukaemia recurrent, delirium, nephropathy toxic, cholecystitis, and proteinuria in 1 subject each (some subjects developed >1 event).
Rescue therapy	Blood creatinine increased in 1 subject.

7.2.2 Japanese phase III study (CTD 5.3.5.2-2: Study 3001 [January 2022 to June 2023])

An open-label, single-group study was conducted in Japan to investigate the efficacy, safety, and PK of maribavir in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance) or asymptomatic CMV viremia (target sample size, approximately 47 subjects [approximately 3 subjects with refractory CMV disease and approximately 44 subjects with asymptomatic CMV viremia]).

Table 48 shows the main inclusion/exclusion criteria in this study.

Table 48. Main inclusion/exclusion criteria

Inclusion criteria	1. Patients of Japanese nationality aged ≥16 years. 2. HSCT or SOT recipients. 3. Patients with CMV infection (plasma CMV DNA level at screening ≥455 UI/mL in 2 consecutive assessments[a)] performed with an interval of ≥1 day) confirmed based on the results of qPCR or an equivalent quantitative CMV DNA test at the central laboratory. 4. Patients with post-HSCT or SOT primary CMV infection or CMV reactivation who requires treatment according to the judgment of the investigator, and who also meet either of the following: • Subjects with refractory CMV disease (with or without genotypic resistance[b)]): Currently having CMV disease refractory[c)] to the recently administered anti-CMV drugs. • Subjects with asymptomatic CMV viremia: Having neither tissue-invasive CMV disease nor CMV syndrome (only for SOT subjects) at baseline, as determined by the investigator according to the criteria of Ljungman et al. (*Clin Infect Dis*. 2017;64:87-91).
Exclusion criteria	1. Patients on treatment with VGCV, GCV, FOS, or letermovir at the start of the study treatment or who are considered to require 1 of these drugs during the 8-week treatment period. 2. Patients determined to have tissue-invasive CMV disease in the central nervous system or CMV retinitis based on the investigator's assessment at screening and before administration at Visit 2 (Day 0). 3. Patients requiring mechanical ventilation or a vasopressor for hemodynamic support at baseline. 4. Patients receiving treatment for acute or chronic hepatitis C.

a) Both specimens were collected within 14 days (1 of them within 5 days) before the first dose of the study drug.
b) Defined as documentation of ≥1 or more CMV gene mutations related to resistance to intravenous GCV, oral VGCV, or intravenous FOS.
c) Defined as documented failure to achieve >1 $\log_{10}$ decrease in plasma CMV DNA level after ≥14 days of treatment with intravenous GCV, oral VGCV, or intravenous FOS.

Maribavir 400 mg was orally administered twice daily for 8 weeks.

All 41 enrolled subjects (3 subjects with refractory CMV disease[45)] and 38 subjects with asymptomatic CMV viremia[46)]) received ≥1 dose of the study treatment, and were included in the full analysis set and the safety analysis population. The full analysis set was used as the efficacy analysis population.

45) 2 HSCT recipients and 1 SOT recipient (1 renal transplant recipient).
46) 34 HSCT recipients and 4 SOT recipients (3 renal transplant recipients and 1 hepatic transplant recipient).

The study treatment was discontinued in 19.5% (8 of 41) of the subjects, and the reasons for treatment discontinuation were consent withdrawal (6 subjects) and death (2 subjects[47)]).

Concerning the efficacy, the proportion of patients achieving confirmed CMV viremia clearance[48)] at Week 8, which was assessed as the primary efficacy endpoint, in HSCT or SOT recipients with refractory CMV disease was 33.3% (1 of 3 subjects).[49)]
Concerning the safety, the incidence of adverse events and adverse drug reactions observed in the on-treatment observation period (until 7 days after the last dose of the study drug) was 87.8% (36 of 41 subjects) and 36.6% (15 of 41 subjects), respectively, in the maribavir-treated subjects. Table 49 shows the adverse events and adverse drug reactions observed in ≥5% of subjects.

Adverse events leading to death occurred in 2.4% (1 of 41) of the maribavir-treated subjects (graft versus host disease), but a causal relationship of the adverse event to the study drug was ruled out.

Serious adverse events occurred in 19.5% (8 of 41) of the maribavir-treated subjects (febrile neutropenia, neutropenia, diarrhoea, melaena, hyperbilirubinaemia, graft versus host disease, graft versus host disease in gastrointestinal tract, cytomegalovirus chorioretinitis, decreased appetite, and bronchitis chronic in 1 subject each [some subjects developed >1 event]). A causal relationship of any of the adverse events to the study drug was not ruled out in 2 subjects (febrile neutropenia and hyperbilirubinaemia in 1 subject each). The event in 1 subject (febrile neutropenia) did not resolve, and hyperbilirubinaemia resolved.

Adverse events leading to treatment discontinuation occurred in 22.0% (9 of 41) of the maribavir-treated subjects (febrile neutropenia, thrombotic microangiopathy, graft versus host disease, cytomegalovirus chorioretinitis, decreased appetite, post transplant lymphoproliferative disorder, depressed level of consciousness, headache, and taste disorder in 1 subject each). Among them, a causal relationship of any of the adverse events to the study drug was not ruled out in 4 subjects (febrile neutropenia, thrombotic microangiopathy, decreased appetite, and headache in 1 subject each). All these events resolved or were resolving, except for the event that did not resolve in 1 subject (febrile neutropenia).

[47)] One subject died during the study treatment, and the other died during the follow-up period (>7 days after the end of the study treatment). For both subjects, a causal relationship of the death to the study drug was ruled out.
[48)] Defined as a condition in which plasma CMV DNA levels were below the LLOQ (34.5 IU/mL) for post-baseline samples, in 2 consecutive assessments separated by ≥5 days (at the central laboratory). The rate in the case of using the same definition as in the foreign phase III study (<137 IU/mL) was set as a secondary endpoint.
[49)] The proportion of patients achieving confirmed CMV viremia clearance at the end of Week 8 in patients with asymptomatic CMV viremia was 71.1% (27 of 38 subjects).

Table 49. Main adverse events and adverse drug reactions (on-treatment observation period ; safety analysis population)

Event	Adverse events Maribavir-treated subjects (N = 41)	Adverse drug reactions Maribavir-treated subjects (N = 41)
Overall	36 (87.8)	15 (36.6)
Nausea	10 (24.4)	6 (14.6)
Anaemia	7 (17.1)	1 (2.4)
Pyrexia	6 (14.6)	1 (2.4)
Headache	6 (14.6)	2 (4.9)
Decreased appetite	5 (12.2)	1 (2.4)
Generalised oedema	4 (9.8)	0
Taste disorder	4 (9.8)	1 (2.4)
Hypertension	3 (7.3)	1 (2.4)
Oedema peripheral	3 (7.3)	1 (2.4)

n (%). MedDRA version 26.0.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package

The applicant's explanation:

When the development of maribavir was initiated in Japan, the preceding foreign phase III study (Study 303) in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance) had been completed, and the foreign phase III study (Study 302) in HSCT recipients with asymptomatic CMV viremia who have not previously been treated with existing anti-CMV therapies was ongoing. Therefore, the initial plan was to obtain approval of maribavir for the indication of CMV disease (regardless of whether it is refractory to existing anti-CMV therapies or has previously been treated) in HSCT or SOT recipients in Japan, by using the results of the Japanese phase III study (Study 3001) in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies or asymptomatic CMV viremia, in addition to the anticipated results of Studies 303 and 302.

However, since the non-inferiority of maribavir to the comparator VGCV could not be demonstrated in Study 302, the applicant considered the construction of a clinical data package for the indication limited to "CMV disease refractory to existing anti-CMV therapies in HSCT or SOT recipients," which is the indication approved in Europe and the US based on the results of Study 303. Although the number of eligible subjects enrolled in Study 3001 was limited (3 subjects), the efficacy and safety of maribavir for the treatment of CMV disease refractory to existing anti-CMV therapies in Japanese HSCT or SOT recipients are deemed explainable based on the following facts:

- The pathophysiology of refractory CMV disease and its diagnostic criteria are similar in Japan and other countries.
- Drugs recommended for the treatment of CMV disease do not substantially differ between Japanese and foreign management guidelines.[50)]
- For the safety evaluation of maribavir treatment, safety information on subjects with asymptomatic CMV viremia obtained in Study 3001 and others can be used because the treatment duration and the dosage regimen are the same.

[50)] *Lancet Infect Dis.* 2019;19(8):e260-e272, *Transplantation.* 2018;102(6):900-931.

Keeping comparison with Study 303 in mind, the evaluation parameters for CMV disease in Study 3001, such as the eligibility criteria for patients with refractory or resistant CMV disease (including the definition of "refractory"), treatment duration, dosage regimen, and primary efficacy endpoint (the proportion of subjects achieving confirmed CMV viremia clearance at Week 8), had originally been matched to those in Study 303 as far as possible. The following differences in the inclusion criteria of the two studies were not considered to affect the comparison of subject populations:

- Although there was a difference in the inclusion criteria for age between the studies (≥12 years in Study 303 vs. ≥16 years in Study 3001), all of the subjects enrolled in Study 303 were aged ≥16 years.
- Although the reference range for CMV DNA was different between the studies (whole blood CMV DNA ≥2,730 IU/mL or plasma CMV DNA ≥910 IU/mL in Study 303 vs. plasma CMV DNA ≥455 IU/mL in Study 3001), all of the subjects with CMV disease refractory to existing anti-CMV therapies enrolled in Study 3001 had plasma CMV DNA levels ≥910 IU/mL.

PMDA's view:

The efficacy and safety of maribavir for the treatment of refractory CMV disease in Japanese organ transplant recipients (including HSCT recipients) can be evaluated based on the submitted clinical study results.

7.R.2 Efficacy

7.R.2.1 Efficacy of maribavir for treatment of CMV disease refractory to existing anti-CMV therapies in HSCT or SOT recipients

The applicant's explanation:

Table 50 shows the results of efficacy evaluation in Study 303. The proportion of subjects achieving confirmed CMV viremia clearance at Week 8, which was assessed as the primary endpoint, was 55.7% (131 of 235 subjects) in the maribavir group and 23.9% (28 of 117 subjects) in the IAT group. The intergroup difference [2-sided 95% CI] was 32.8 [22.80, 42.74], showing a statistically significant difference. Thus, the superiority of maribavir over IAT was demonstrated. The proportion of subjects with achievement of CMV viremia clearance and infection symptom control[51)] at Week 8, followed by maintenance of the treatment effects for a certain period also tended to be consistently higher in the maribavir group than in the IAT group.

Table 50. Key efficacy evaluation results in Study 303 (regardless of completion of 8-week study treatment; efficacy analysis population)

	Maribavir (N = 235)	IAT (N = 117)
Proportion of subjects achieving confirmed CMV viremia clearance at Week 8 (primary endpoint)	131 (55.7)	28 (23.9)
Proportion of subjects with achievement of CMV viremia clearance and infection symptom control[a)] at Week 8, followed by maintenance of the treatment effects through Week 12	53 (22.6)	12 (10.3)
Proportion of subjects with achievement of CMV viremia clearance and infection symptom control[a)] at Week 8, followed by maintenance of the treatment effects through Week 16	44 (18.7)	12 (10.3)
Proportion of subjects with achievement of CMV viremia clearance and infection symptom control[a)] at Week 8, followed by maintenance of the treatment effects through Week 20	43 (18.3)	11 (9.4)

No. of subjects (%)

a) Resolution or improvement of tissue-invasive CMV disease or CMV syndrome in subjects with symptomatic CMV disease at baseline, or maintenance of an asymptomatic state in subjects with asymptomatic CMV viremia.

[51)] Resolution or improvement of tissue-invasive CMV disease or CMV syndrome in subjects with symptomatic CMV disease at baseline, or maintenance of an asymptomatic state in subjects with asymptomatic CMV viremia.

Table 51 shows the proportion of subjects achieving confirmed CMV viremia clearance at Week 8 by characteristics of subjects enrolled in Study 303. The results show a generally similar trend to that in the overall population.

Table 51. Proportion of subjects achieving confirmed CMV viremia clearance at Week 8 by patient characteristics in Study 303 (efficacy analysis population)

		Maribavir (N = 235)	IAT (N = 117)
Sex	Male	58.8 (87/148)	23.1 (16/65)
	Female	50.6 (44/87)	25.0 (13/52)
Age	18 to 44 years	50.9 (28/55)	25.0 (8/32)
	45 to 64 years	56.3 (71/126)	27.5 (19/69)
	≥65 years	59.3 (32/54)	6.3 (1/16)
Transplantation type	HSCT	55.9 (52/93)	20.8 (10/48)
	SOT	55.6 (79/142)	26.1 (18/69)
Transplanted organ	Heart	42.9 (6/14)	11.1 (1/9)
	Lung	47.5 (19/40)	13.6 (3/22)
	Liver	100 (6/6)	0 (0/1)
	Pancreas	0 (0/2)	Not applicable
	Small intestine	0 (0/1)	Not applicable
	Kidney	59.5 (44/74)	34.4 (11/32)
	Multiple organs	80.0 (4/5)	60.0 (3/5)
Mutations resistant to anti-CMV drugs other than maribavir at baseline	Present	62.8 (76/121)	20.3 (14/69)
	Absent	43.8 (42/96)	32.4 (11/34)
Symptomatic CMV disease	Present	47.6 (10/21)	12.5 (1/8)
	Absent	56.5 (121/214)	24.8 (27/109)
Anti-CMV antibody in the donor and recipient[a)]	D+/R+	56.6 (30/53)	28.0 (7/25)
	D+/R−	56.3 (71/126)	28.8 (17/59)
	D−/R+	57.1 (24/42)	11.1 (3/27)
	D−/R−	50.0 (6/12)	25.0 (1/4)

The proportion of subjects achieving confirmed CMV viremia clearance (%) (No. of subjects achieving confirmed CMV viremia clearance / No. of subjects evaluated)

a) Data were missing in 2 subjects each in the maribavir and IAT group. D = donner; R = recipient; + = CMV antibody positive; - = CMV antibody negative.

Among the HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance) enrolled in Study 3001, the proportion of subjects achieving confirmed CMV viremia clearance at Week 8, which was assessed as the primary efficacy endpoint, was 33.3% (1 of 3 subjects), and CMV viremia clearance and infection symptom control in this subject were maintained through Week 20. Although there are limitations to the comparison because the number of Japanese organ transplant recipients with refractory CMV disease was limited (3 subjects), the results do not deny the efficacy of maribavir in Japanese patients for the following reasons:

- The efficacy of maribavir by patient characteristics in Study 303 (Table 51) tended to be consistently higher in the maribavir group than in the IAT group.
- In 1 HSCT recipient who failed to achieve the primary endpoint, the symptoms of tissue-invasive CMV disease that had been present at screening were improving during treatment with maribavir.
- In 1 SOT recipient, a certain level of antiviral activity (trend toward a decrease in CMV DNA level) was observed with maribavir treatment, and the symptoms of tissue-invasive CMV disease that had been present at screening were improving during treatment with maribavir.

Although patients with CMV disease refractory to existing anti-CMV therapies in non-renal SOT recipients were not enrolled in Study 3001, the efficacy of maribavir can be expected in non-renal organ transplant recipients, as in renal transplant recipients, in view of the following points:

- Since maribavir targets the protein kinase encoded by the UL97 gene and acts directly on CMV in the plasma or invaded tissues, a difference in the transplanted organ is unlikely to affect the pharmacological action of maribavir.
- While maribavir is mainly absorbed from the gastrointestinal tract and eliminated by CYP3A4-mediated hepatic metabolism, the PK of maribavir is not affected by transplantation type (HSCT or SOT) or the type of SOT (kidney, lung, liver, or heart) [see Section 6.2.6]. Therefore, the PK of maribavir is considered to be constant in the presence of stable hepatic function, regardless of the transplantation type (including the type of SOT).
- Subgroup analysis by the type of SOT in Study 303 showed that the efficacy in the maribavir group was consistently higher than that in the IAT group in all subgroups of subjects who received kidney, lung, heart, liver, or multiple organ transplants.

In view of the above, the efficacy of maribavir can also be promising for the treatment of CMV disease refractory to existing anti-CMV therapies in Japanese organ transplant recipients (including HSCT recipients).

PMDA's view:
In Study 3001, although the number of enrolled Japanese patients with CMV disease refractory to existing anti-CMV therapies was limited (3 subjects), a trend toward improvement was observed in individual patients. In Study 303, the superiority of maribavir over IAT was demonstrated, and the efficacy was consistent regardless of the patient characteristics. The applicant's explanation is therefore understandable in that the efficacy of maribavir can also be promising for the treatment of refractory CMV disease in Japanese organ transplant recipients (including HSCT recipients).

However, clinical experience with use of maribavir in Japanese HSCT and SOT recipients with CMV disease refractory to existing anti-CMV therapies is extremely limited, and there is no information on the efficacy of maribavir in non-renal SOT recipients. Information on the efficacy of maribavir should therefore be continuously collected in the post-marketing setting, and all obtained information should appropriately be provided to healthcare professionals.

In addition, since known maribavir-resistant amino acid substitutions were observed during or after maribavir treatment [see Section 3.1.3.3], physicians should be advised to consider whether to continue maribavir treatment in patients with no response to maribavir, in light of the possibility of development of maribavir resistance.

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

7.R.3 Safety

7.R.3.1 Safety profile of maribavir

The applicant's explanation:

Table 52 shows a summary of the safety results of the foreign phase II study (Study 202), Study 303, and Study 3001 in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies (with or without genotypic resistance). Table 53 shows adverse events reported in ≥10% of subjects in any treatment group (or maribavir-treated subjects) of these studies.

Table 52. Summary of safety (on-treatment observation period; safety analysis population)[a)]

	Study 202			Study 303		Study 3001
	Maribavir 400 mg BID (N = 40)	Maribavir 800 mg BID (N = 40)	Maribavir 1,200 mg BID (N = 40)	Maribavir group (N = 234)	IAT (N = 116)	Maribavir-treated subjects (N = 41)
Duration of study drug exposure (days)	85.2 [9, 177]	86.0 [7, 173]	89.1 [5, 176]	48.6 [1, 60]	31.2 [3, 59]	49.7 [2, 59]
Adverse events	40 (100)	40 (100)	40 (100)	228 (97.4)	106 (91.4)	36 (87.8)
Adverse drug reactions	31 (77.5)	32 (80.0)	30 (75.0)	141 (60.3)	57 (49.1)	15 (36.6)
Serious adverse events	28 (70.0)	27 (67.5)	26 (65.0)	90 (38.5)	43 (37.1)	8 (19.5)
Adverse events leading to death	10 (25.0)	12 (30.0)	10 (25.0)	16 (6.8)	6 (5.2)	1 (2.4)
Adverse events leading to treatment discontinuation	11 (27.5)	17 (42.5)	13 (32.5)	31 (13.2)	37 (31.9)	9 (22.0)

n (%). MedDRA version: 17.0 for Study 202, 23.0 for Study 303, and 26.0 for Study 3001. No. of days of exposure: mean [range].

a) The duration of treatment was up to 24 weeks in Study 202, and up to 8 weeks in Studies 303 and 3001. For all studies, the treatment duration covered the time from the first dose of the study drug to 7 days after the last dose.

Table 53. Adverse events reported in ≥10% of subjects in any treatment group (or maribavir-treated subjects) of the studies (on-treatment observation period; safety analysis population)[a)]

	Study 202			Study 303		Study 3001
	Maribavir 400 mg BID (N = 40)	Maribavir 800 mg BID (N = 40)	Maribavir 1,200 mg BID (N = 40)	Maribavir (N = 234)	IAT (N = 116)	Maribavir-treated subjects (N = 41)
Duration of study drug exposure (days)	85.2 [9, 177]	86.0 [7, 173]	89.1 [5, 176]	48.6 [1, 60]	31.2 [3, 59]	49.7 [2, 59]
Overall	40 (100)	40 (100)	40 (100)	228 (97.4)	106 (91.4)	36 (87.8)
Dysgeusia[b)]	24 (60.0)	25 (62.5)	29 (72.5)	87 (37.2)	4 (3.4)	2 (4.9)
Nausea	15 (37.5)	12 (30.0)	14 (35.0)	50 (21.4)	25 (21.6)	10 (24.4)
Vomiting	11 (27.5)	13 (32.5)	11 (27.5)	33 (14.1)	19 (16.4)	1 (2.4)
Oedema peripheral	11 (27.5)	6 (15.0)	6 (15.0)	17 (7.3)	9 (7.8)	3 (7.3)
Headache	9 (22.5)	4 (10.0)	6 (15.0)	19 (8.1)	15 (12.9)	6 (14.6)
Fatigue	8 (20.0)	10 (25.0)	7 (17.5)	28 (12.0)	10 (8.6)	0
Anaemia	7 (17.5)	7 (17.5)	10 (25.0)	29 (12.4)	14 (12.1)	7 (17.1)
Rash	7 (17.5)	6 (15.0)	3 (7.5)	8 (3.4)	1 (0.9)	0
Cytomegalovirus infection	6 (15.0)	12 (30.0)	10 (25.0)	10 (4.3)	4 (3.4)	0
Pneumonia	6 (15.0)	4 (10.0)	5 (12.5)	8 (3.4)	2 (1.7)	0
Urinary tract infection	6 (15.0)	3 (7.5)	3 (7.5)	9 (3.8)	5 (4.3)	0
Pyrexia	6 (15.0)	6 (15.0)	3 (7.5)	24 (10.3)	17 (14.7)	6 (14.6)
Diarrhoea	5 (12.5)	13 (32.5)	10 (25.0)	44 (18.8)	24 (20.7)	2 (4.9)
Cough	5 (12.5)	6 (15.0)	2 (5.0)	13 (5.6)	7 (6.0)	0
Constipation	5 (12.5)	5 (12.5)	5 (12.5)	9 (3.8)	7 (6.0)	1 (2.4)
Hypotension	5 (12.5)	5 (12.5)	1 (2.5)	7 (3.0)	3 (2.6)	0
Dehydration	5 (12.5)	4 (10.0)	3 (7.5)	3 (1.3)	0	0
Pruritus	5 (12.5)	1 (2.5)	5 (12.5)	5 (2.1)	0	2 (4.9)
Immunosuppressant drug level increased	4 (10.0)	2 (5.0)	6 (15.0)	21 (9.0)	1 (0.9)	1 (2.4)
Dyspnoea	4 (10.0)	2 (5.0)	5 (12.5)	13 (5.6)	8 (6.9)	0
Clostridium difficile infection	4 (10.0)	2 (5.0)	4 (10.0)	1 (0.4)	0	0
Back pain	4 (10.0)	1 (2.5)	4 (10.0)	11 (4.7)	3 (2.6)	0
Renal impairment	3 (7.5)	7 (17.5)	9 (22.5)	1 (0.4)	3 (2.6)	0
Decreased appetite	3 (7.5)	5 (12.5)	4 (10.0)	18 (7.7)	9 (7.8)	5 (12.2)
Abdominal pain	3 (7.5)	4 (10.0)	3 (7.5)	18 (7.7)	3 (2.6)	1 (2.4)
Depression	2 (5.0)	8 (20.0)	1 (2.5)	2 (0.9)	3 (2.6)	0
Hypokalaemia	2 (5.0)	4 (10.0)	6 (15.0)	8 (3.4)	11 (9.5)	1 (2.4)
Acute graft versus host disease	2 (5.0)	4 (10.0)	3 (7.5)	2 (0.9)	0	0
Hyperkalaemia	2 (5.0)	3 (7.5)	5 (12.5)	8 (3.4)	2 (1.7)	0
Weight decreased	2 (5.0)	3 (7.5)	4 (10.0)	7 (3.0)	2 (1.7)	1 (2.4)
Dizziness	1 (2.5)	5 (12.5)	3 (7.5)	17 (7.3)	5 (4.3)	1 (2.4)
Cytomegalovirus viraemia	0	0	0	24 (10.3)	6 (5.2)	0
Neutropenia	2 (5.0)	1 (2.5)	2 (5.0)	22 (9.4)	26 (22.4)	1 (2.4)

n (%). MedDRA version: 17.0 for Study 202, 23.0 for Study 303, and 26.0 for Study 3001. No. of days of exposure: mean [range].

a) The duration of treatment was up to 24 weeks in Study 202, and up to 8 weeks in Studies 303 and 3001. For all studies, the treatment duration covered the time from the first dose of the study drug to 7 days after the last dose.

b) No. of subjects with dysgeusia for Study 202, and No. of subjects with dysgeusia for Studies 303 and 3001.

The incidence of adverse events in Study 303 was similar in the maribavir group and the IAT group, namely, >90% in both, and the incidences of the most common adverse events were also generally similar in these groups, except for dysgeusia, cytomegalovirus viraemia, immunosuppressant drug level increased, and abdominal pain. The incidence of adverse drug reactions tended to be higher in the maribavir group, but most of them were dysgeusia. The incidences of serious adverse events and adverse events leading to death in the maribavir group were similar to those in the IAT group. The incidence of adverse events leading to treatment discontinuation was lower in the maribavir group than in the IAT group.

The incidence of adverse events in Study 202 was similar to that in Study 303, but the incidence of serious adverse events, adverse events leading to death, and adverse events leading to treatment discontinuation tended to be higher in Study 202. This was considered attributable to the difference in the duration of exposure,

because the duration of treatment with the study drug was specified as up to 24 weeks in Study 202. In addition, the observed adverse events were similar in the maribavir 400 mg BID group, maribavir 800 mg BID group, and maribavir 1,200 mg BID group, and the safety profile did not change with increasing dose.

The summary of safety in Study 3001 is described. The incidence of adverse events in Study 3001 was similar to or tended to be lower than that in Study 303, except for adverse events leading to treatment discontinuation, and there were no trends of particular concern in Japanese subjects. In addition, the analysis of individual events identified no events with a higher incidence specific to Japanese subjects.

Table 54 shows the summary of safety in Studies 203 and 302 in HSCT or SOT recipients with asymptomatic CMV viremia. The safety profile of maribavir did not greatly differ from that in Studies 202, 303, and 3001.

Table 54. Summary of safety in Studies 203 and 302 (on-treatment observation period; safety analysis population)[a)]

	Study 203				Study 302	
	Maribavir 400 mg BID (N = 40)	Maribavir 800 mg BID (N = 40)	Maribavir 1,200 mg BID (N = 39)	VGCV[b)] (N = 40)	Maribavir (N = 273)	VGCV[c)] (N = 274)
Duration of study drug exposure (days)	50.8 [1, 92]	48.0 [3, 88]	48.1 [2, 88]	43.1 [1, 88]	44.1 [1, 62]	40.4 [1, 60]
Adverse events	39 (97.5)	38 (95.0)	39 (100)	33 (82.5)	268 (98.2)	269 (98.2)
Adverse drug reactions	25 (62.5)	25 (62.5)	30 (76.9)	9 (22.5)	148 (54.2)	168 (61.3)
Serious adverse events	18 (45.0)	20 (50.0)	21 (53.8)	15 (37.5)	88 (32.2)	95 (34.7)
Adverse events leading to death	2 (5.0)	1 (2.5)	3 (7.7)	3 (7.5)	18 (6.6)	12 (4.4)
Adverse events leading to treatment discontinuation	12 (30.0)	5 (12.5)	10 (25.6)	5 (12.5)	76 (27.8)	113 (41.2)

n (%). MedDRA version: 17.0 for Study 203 and 23.0 for Study 302. No. of days of exposure: mean [range].

a) The duration of treatment was up to 12 weeks in Study 203, and up to 8 weeks in Study 302. For both studies, the treatment duration covered the time from the first dose of the study drug to 7 days after the last dose.

b) The dose of VGCV was adjusted according to renal function.

c) The dose of VGCV was selected from 900 mg BID, 450 mg BID, or 450 mg QD according to renal function.

According to the foreign post-marketing safety information,[52)] there were 216 spontaneous reports of serious adverse drug reactions. The most common events were death (28 reports), hospitalisation (18 reports), cytomegalovirus infection (16 reports), cytomegalovirus viraemia (7 reports), sepsis (5 reports), cytomegalovirus infection reactivation (5 reports), and acute kidney injury (5 reports), pneumonia (4 reports), and each of cytomegalovirus chorioretinitis (3 reports), cytomegalovirus colitis (3 reports), infection (3 reports), and leukopenia (3 reports). No new safety concerns have been identified by the end of the reporting period.

In view of the above, treatment with maribavir is tolerable, and no clinically significant safety concerns have been identified.

On the basis of the submitted study results, PMDA confirmed that the safety profile of maribavir is not substantially different from that of existing drugs, and no new safety concerns specific to Japanese patients have been identified. However, since taste disorder (taste disturbance) was frequently reported as an event specific to maribavir, the event was further investigated, as described in the next section.

[52)] Events accrued from November 23, 2021 to November 22, 2023 (approximately 16,166 thousand person-years).

7.R.3.2 Taste disorder (taste disturbance)

The applicant's explanation:

Table 55 and Table 56 show the incidence of adverse events and adverse drug reactions related to taste disorder (taste disturbance) from the first dose of the study drug to 7 days after the last dose in Studies 202, 203, 302, 303, and 3001.

Table 55. Incidence of adverse events and adverse drug reactions related to taste disorder (taste disturbance)[a] (on-treatment observation period; safety analysis population)

	Study 202			Study 303		Study 3001
	Maribavir 400 mg BID (N = 40)	Maribavir 800 mg BID (N = 40)	Maribavir 1,200 mg BID (N = 40)	Maribavir (N = 234)	IAT (N = 116)	Maribavir-treated subjects (N = 41)
Duration of study drug exposure (days)	85.2 [9, 177]	86.0 [7, 173]	89.1 [5, 176]	48.6 [1, 60]	31.2 [3, 59]	49.7 [2, 59]
Adverse events	24 (60.0)	25 (62.5)	29 (72.5)	108 (46.2)	5 (4.3)	6 (14.6)
Adverse drug reactions	24 (60.0)	25 (62.5)	29 (72.5)	103 (44.0)	2 (1.7)	3 (7.3)
Death	0	0	0	0	0	0
Serious adverse events	0	0	0	0	0	0
Severe or most severe events	0	1 (2.5)	0	1 (2.4)	0	0
Adverse events leading to treatment discontinuation	0	0	1 (2.5)	2 (0.9)	0	1 (2.4)

n (%). MedDRA version: 17.0 for Study 202, 23.0 for Study 303, and 26.0 for Study 3001. No. of days of exposure mean [range].

a) Study 202: Adverse events classified as MedDRA Preferred Term (PT) "Ageusia," "Dysgeusia," or "Hypogeusia." Studies 303 and 3001: Adverse events classified as MedDRA PT "Ageusia," "Dysgeusia," "Hypogeusia" or "Taste disorder."

Table 56. Incidence of adverse events and adverse drug reactions related to taste disorder (taste disturbance)[a] (on-treatment observation period; safety analysis population)

	Study 203[b]				Study 302[b]	
	Maribavir 400 mg BID (N = 40)	Maribavir 800 mg BID (N = 40)	Maribavir 1,200 mg BID (N = 39)	VGCV[c] (N = 40)	Maribavir (N = 273)	VGCV[d] (N = 274)
Duration of study drug exposure (days)	50.8 [1, 92]	48.0 [3, 88]	48.1 [2, 88]	43.1 [1, 88]	44.1 [1, 62]	40.4 [1, 60]
Adverse events	18 (45.0)	17 (42.5)	15 (38.5)	1 (2.5)	70 (25.6)	24 (8.8)
Adverse drug reactions	18 (45.0)	17 (42.5)	15 (38.5)	0	58 (21.2)	18 (6.6)
Death	0	0	0	0	0	0
Serious adverse events	0	0	0	0	0	0
Severe or most severe events	0	0	0	0	1 (0.4)	0
Adverse events leading to treatment discontinuation	0	0	0	0	6 (2.2)	1 (0.4)

n (%). MedDRA version: 17.0 for Study 203 and 23.0 for Study 302. No. of days of exposure [range].

a) Study 203: Adverse events classified as MedDRA PT "Ageusia," "Dysgeusia," or "Hypogeusia." Study 302: Adverse events classified as MedDRA PT "Ageusia," "Dysgeusia," "Hypogeusia," or "Taste disorder."

b) The duration of treatment was up to 12 weeks in Study 203, and up to 8 weeks in Study 302. For both studies, the treatment duration covered the time from the first dose of the study drug to 7 days after the last dose.

c) The dose of VGCV was adjusted according to renal function.

d) The dose of VGCV was selected from 900 mg BID, 450 mg BID, or 450 mg QD according to renal function.

In Japanese and foreign phase II and phase III studies, events related to taste disorder (taste disturbance) were frequently observed, but there were no deaths or serious adverse events, and most of the observed adverse events were mild or moderate. Adverse events leading to treatment discontinuation were observed in 1 subject (2.5%) in the maribavir 1,200 mg BID group in Study 202, 2 subjects (0.9%) in the maribavir group in Study 303, 1 subject (2.4%) in Study 3001, and 6 subjects (2.2%) in Study 302. In the maribavir group and the maribavir-treated rescue group in Study 303, of 119 subjects with taste disorder/dysgeusia, 44 subjects (37.0%) recovered during treatment, with a median time to resolution of 43 days (range, 7-59 days). Furthermore, of 75

subjects with taste disorder persisting at the end of maribavir treatment, 67 subjects (89.3%) recovered, with a median time to resolution of 6 days.

In view of the above, since most of the taste disorder (taste disturbance) events observed in clinical studies were mild and resolved during or after maribavir treatment, the safety and tolerability of maribavir are acceptable.

PMDA's view:
The applicant's position on events related to taste disorder (taste disturbance) is understandable in that the safety and tolerability of maribavir are acceptable.

PMDA's conclusion about the safety of maribavir:
In view of the results of Studies 202, 303, and 3001, and other findings, the safety of maribavir in patients with post-transplantation, refractory CMV disease is acceptable. Data obtained to date confirmed that no events of concern specific to Japanese patients have been identified. However, since the clinical experience with use of maribavir in Japanese patients with post-transplantation CMV disease is limited, information on the safety of maribavir should be continuously collected in the post-marketing setting, and the obtained information should appropriately be provided to healthcare professionals.

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

7.R.4 Clinical positioning

On the basis of the considerations in Sections 7.R.2 and 7.R.3, PMDA has concluded that maribavir can be a new treatment option for organ transplant recipients (including HSCT recipients) with CMV disease refractory to existing anti-CMV therapies.

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

7.R.5 Indication

PMDA's view:
On the basis of the considerations in Sections 7.R.1, 7.R.2, 7R.3, and 7.R.4, and considering that the clinical experience with use of maribavir in Japanese HSCT or SOT recipients with CMV disease is extremely limited and that the non-inferiority of maribavir to the first-line drug VGCV was not demonstrated in the foreign phase III study (Study 302) in patients with asymptomatic CMV viremia who had not previously been treated with existing anti-CMV therapies, the indication should be modified to clearly specify the target patient population, as with the approved indication outside Japan, as described below.

Indication
~~Treatment of~~ cytomegalovirus disease refractory to existing anti-cytomegalovirus therapies in organ transplant recipients (including hematopoietic stem cell transplant recipients)

(The underlined words are added to, and the strikethrough words are deleted from the proposed text.)

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

7.R.6 Dosage and administration

PMDA has concluded that the dosage and administration of maribavir may be set as "The usual adult dosage is 400 mg of maribavir administered orally, twice daily," as proposed by the applicant, based on the following:

The applicant's explanation about the duration of treatment with maribavir:
The Japanese management guidelines recommend that anti-CMV drugs in the treatment of CMV disease should be administered for at least 2 weeks until the achievement of clinical improvement and CMV viremia clearance. In Study 202, the proportion of subjects achieving confirmed CMV viremia clearance within 6 weeks of maribavir treatment was 70.0% in the maribavir 400 mg BID group, 62.5% in the maribavir 800 mg BID group, and 67.5% in the maribavir 1,200 mg BID group, suggesting a certain level of the efficacy of maribavir. However, since continued use of immunosuppressants may lead to relapse of CMV viremia, a total of 8 weeks, consisting of 6 weeks of the initial treatment plus 2 weeks of continued therapy after CMV viremia clearance, was set as the duration of treatment in Studies 303 and 3001.

The Japanese management guidelines also point out the importance of determining the duration of treatment with anti-CMV drugs in the treatment of symptomatic CMV disease, considering treatment response for each patient and organ and individual patient risks. It is therefore considered difficult to specify the duration of treatment uniformly in the package insert. The results of evaluation of the incidence of delayed adverse events and adverse drug reactions based on the safety profile in each observation period in Study 202, in which maribavir administration was allowed for up to 24 weeks, showed that there is no relationship between the duration of maribavir treatment and the incidence of adverse events or adverse drug reactions (Table 57), with no specific delayed adverse events.

In view of the above, the long-term use of maribavir is unlikely to raise significant safety concerns. Therefore, precautions regarding the specific recommended duration of treatment are unnecessary in the package insert, and the treatment duration should be determined based on the condition of individual patients.

Table 57. Summary of safety by observation period[a] (Study 202; on-treatment observation period; safety analysis population)

	Overall	≤8 weeks of treatment	>8 to ≤16 weeks of treatment	>16 weeks of treatment
Adverse events	100 (120/120)	99.2 (119/120)	87.2 (68/78)	81.0 (34/42)
Adverse drug reactions	77.5 (93/120)	74.2 (89/120)	24.0 (18/75)	22.0 (9/41)
Serious adverse events	67.5 (81/120)	53.3 (64/120)	36.8 (28/76)	34.1 (14/41)
Adverse events leading to death	20.0 (24/120)	15.8 (19/120)	4.0 (3/75)	4.9 (2/41)
Adverse events leading to treatment discontinuation	33.3 (40/120)	16.7 (20/120)	20.0 (15/75)	12.2 (5/41)

% (n/N)

a) To calculate the incidence of adverse events for each observation period, the number of subjects treated with the study drug during the period concerned or the number of subjects with adverse events, serious adverse events, adverse events leading to death, adverse events leading to treatment discontinuation, or adverse drug reactions during the period concerned was used as the denominator.

PMDA's view:

In view of the applicant's explanation, the decision not to provide a specific recommended duration of treatment with maribavir in the package insert, is acceptable. Considering that maribavir may be administered for >24 weeks based on the patient's condition in medical practice, information on the safety and efficacy by treatment period should be collected in post-marketing surveillance, and new findings should be provided to healthcare professionals immediately when they become available.

The above PMDA's conclusion on the dosage and administration will be discussed at the Expert Discussion.

7.R.7 Post-marketing investigation

The applicant's plan about the post-marketing surveillance of maribavir:

General use-results survey (all-case surveillance)

- Safety, efficacy, and clinical course in the clinical setting in Japanese patients
- Type of organ transplantation, use of immunosuppressants, and safety by patient characteristics such as blood concentration (especially serious adverse drug reactions due to increased immunosuppressant concentration)

PMDA's view:

The following information should also be collected in post-marketing surveillance:

- Development of treatment-resistant CMV after maribavir administration
- Safety of >8-week treatment

In addition, information on maribavir-sensitive or resistant mutations in Japanese and foreign clinical isolates, including the published literature, should be collected in the post-marketing setting.

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

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

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

The new drug application data were subjected to document-based inspection and data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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.

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

The new drug application data (CTD 5.3.5.2-2) were subjected to on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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.

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

On the basis of the data submitted, PMDA has concluded that maribavir has efficacy in the treatment of CMV disease refractory to existing anti-CMV therapies in organ transplant recipients (including HSCT recipients), and that maribavir has acceptable safety in view of its benefits. Maribavir, an anti-CMV drug containing a new active ingredient with a new mechanism of action, is clinically meaningful because it offers a new treatment option for patients with CMV disease refractory to existing anti-CMV therapies.

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

Review Report (2)

May 15, 2024

Product Submitted for Approval

Brand Name	Livtencity Tablets 200 mg
Non-proprietary Name	Maribavir
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	November 17, 2023

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 product 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 conclusions described in Sections "7.R.2 Efficacy," "7.R.3 Safety," "7.R.4 Clinical positioning," "7.R.5 Indication," "7.R.6 Dosage and administration," and "7.R.7 Post-marketing investigation" of the Review Report (1).

1.1 Risk management plan (draft)

On the basis of the reviews in the Review Report (1) and the discussions at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for maribavir should include the safety and efficacy specifications presented in Table 58, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 59 and Table 60.

Table 58. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• Increased incidence of serious adverse drug reactions due to increased immunosuppressant concentration	None
Efficacy specification		
• Incidence of clinical treatment-resistant CMV		

Table 59. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance)	• Specified use-results survey (all-case surveillance)	• Provision of information collected through early post-marketing phase vigilance

Table 60. Outline of the specified use-results survey (draft)

Objective	Investigation of the safety and efficacy of maribavir in the clinical setting (development of clinical treatment-resistant CMV)
Survey method	Central registry (all-case surveillance)
Population	Organ transplant recipients (including HSCT recipients) with CMV disease refractory to existing anti-CMV therapies who were treated with maribavir
Observation period	27 weeks from the start of maribavir treatment, or to 7 days after the last dose if the treatment is ongoing at 27 weeks of treatment (Observation period for adverse events continues to 7 days after the last dose, regardless of the duration of treatment)
Planned sample size	250 patients
Main survey items	Patient characteristics, details of treatment, CMV activity, status of CMV disease, status of other infections than CMV infection, incidence of clinical treatment-resistant CMV, transplant rejection, survival, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, under the following conditions. Since the product is an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

~~Treatment of~~ cytomegalovirus disease refractory to existing anti-cytomegalovirus therapies in organ transplant recipients (including hematopoietic stem cell transplant recipients)

(The underlined words are added to, and the strikethrough words are deleted from, the proposed text.)

Dosage and Administration

The usual adult dosage is 400 mg of maribavir administered orally twice daily.

(No change from the proposed text.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a very limited number of Japanese subjects participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a certain number of patients have been accrued. The purposes of the survey are to identify the characteristics of these patients and to collect safety and efficacy data on the product without delay, thereby taking the necessary actions to facilitate the proper use of the product.

Appendix

List of Abbreviations

ACV	Acyclovir
A/G	Albumin/globulin ratio
ALP	Alkaline phosphatase
ARPEp	Human retinal pigment epithelial cell line expressing platelet-derived growth factor α receptor
AUC	Area under the concentration versus time curve
AUC_{inf}	Area under the concentration-time curve from 0 to infinity post dose
$AUC_{0\text{-}t\ h}$	Area under the concentration-time curve from time 0 to t hours post-dose
AUC_{τ}	Area under the concentration-time curve over the dosing interval
BA	Bioavailability
BCRP	Breast cancer resistance protein
BID	*bis in die*
BMI	Body mass index
BSEP	Bile salt export pump
C2BBel	Clone of Caco-2 cell line
Caco-2	Human epithelial colorectal adenocarcinoma
CDV	Cidofovir
CL	Clearance
CLcr	Creatinine clearance
CL_{int}	Intrinsic clearance
C_{max}	Maximum plasma concentration
CMV	Cytomegalovirus
C_{trough}	Trough concentration
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
EC_{50}	50% effective concentration
FOS	Foscarnet
gB	Glycoprotein B
GCV	Ganciclovir
HEK	Human embryonic kidney
HEL	Human embryonic lung cell line
HPLC	High performance liquid chromatography
HSCT	Hematopoietic stem cell transplantation
IAT	Investigator-assigned anti-CMV treatment
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH M7 guideline	Partial Revision of “Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” (PSEHB/PED Notification No. 0627-1 dated June 27, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LTV	Letermovir
MATE	Multidrug and toxin extrusion
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
MPE	Mean photo effect
MRC-5	Human lung fibroblast cell line
MRHF	Human foreskin fibroblast cell line

OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBPK	Physiologically based pharmacokinetic
PFU	Plaque-forming unit
P-gp	P-glycoprotein
PIF	Photo irritation factor
PK	Pharmacokinetics
PPK	Population pharmacokinetics
QD	*quaque die*
QTc	Corrected QT interval
QTcIb	QT rate-corrected individually with placebo QT/RR interval
SCID mouse	Severe combined immunodeficient mouse
SOT	Solid organ transplant
$t_{1/2}$	Estimate of the terminal half-life
t_{max}	Time to reach maximum plasma concentration
UGT	Uridine 5′ diphospho glucuronosyltransferase
UL	Unique long
VGCV	Valganciclovir
V_{ss}	Volume of distribution at steady state
PMDA	Pharmaceuticals and Medical Devices Agency
Japanese management guidelines	Organ transplantation-related CMV disease guideline and HSCT-related CMV disease guideline
Organ transplantation-related CMV disease guideline	Guideline for the Management of Organ Transplantation-related Cytomegalovirus Disease 2022. Drafting Committee for Guideline for the Management of Organ Transplantation-related Cytomegalovirus Infection, the Japan Society for Transplantation, ed.
HSCT-related CMV disease guideline	Guideline for Hematopoietic Cell Transplantation: Treatment and Prevention of Viral Infections—Cytomegalovirus Disease (5th Edition). 2022; Japanese Society for Transplantation and Cellular Therapy Guideline Committee, the Japanese Society for Transplantation and Cellular Therapy, ed.
Study 202	Study SHP620-202 (foreign phase II clinical study in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies [with or without genotypic resistance])
Study 203	Study SHP620-203 (foreign phase II clinical study in HSCT or SOT recipients with asymptomatic CMV viremia)
Study 302	Study SHP620-302 (foreign phase III clinical study in HSCT recipients with asymptomatic CMV viremia who have not previously been treated with existing anti-CMV therapies)
Study 303	Study SHP620-303 (foreign phase III clinical study in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies [with or without genotypic resistance])
Study 3001	Study TAK-620-3001 (Japanese phase III clinical study in HSCT or SOT recipients with CMV disease refractory to existing anti-CMV therapies [with or without genotypic resistance] or asymptomatic CMV viremia)