Report on the Deliberation Results

June 7, 2017

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

Brand Name	Amenalief Tab. 200 mg
Non-proprietary Name	Amenamevir (JAN*)
Applicant	Maruho Co., Ltd.
Date of Application	April 27, 2016

Results of Deliberation

In its meeting held on May 30, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

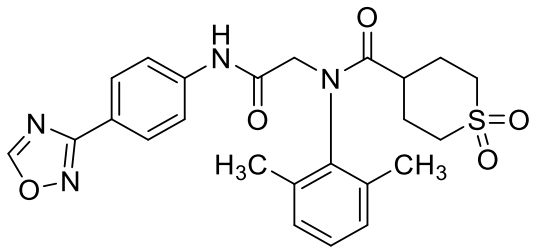
**Japanese Accepted Name (modified INN)*

Review Report

May 8, 2017
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	Amenalief Tab. 200 mg
Non-proprietary Name	Amenamevir
Applicant	Maruho Co., Ltd.
Date of Application	April 27, 2016
Dosage Form/Strength	Tablets: Each tablet contains 200 mg of Amenamevir.
Application Classification	Prescription drug (1), Drug with a new active ingredient
Chemical Structure	



Molecular formula: $C_{24}H_{26}N_4O_5S$
Molecular weight: 482.55
Chemical name: *N*-(2,6-Dimethylphenyl)-*N*-(2-{[4-(1,2,4-oxadiazol-3-yl)phenyl]amino}- 2-oxoethyl)-1,1-dioxothiane-4-carboxamide

Items Warranting Special Mention None

Reviewing Office Office of New Drug IV

Results of Review
On the basis of he data submitted, PMDA has concluded that the product has efficacy in the treatment of herpes zoster, 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 condition.

Indication
Herpes zoster

Dosage and Administration
The usual adult dosage is 400 mg of amenamevir administered orally once daily after a meal.

Condition of Approval
The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

March 1, 2017

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

Product Submitted for Approval

Brand Name	Amenalief Tab. 200 mg
Non-proprietary Name	Amenamevir
Applicant	Maruho Co., Ltd.
Date of Application	April 27, 2016
Dosage Form/Strength	Tablets: Each tablet contains 200 mg of Amenamevir.
Proposed Indication	Herpes zoster
Proposed Dosage and Administration	The usual adult dosage is 400 mg of amenamevir administered orally once daily after a meal.

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List of Abbreviations

ACV	Aciclovir
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Amenalief	Amenalief Tab. 200 mg
Amenamevir	Amenamevir
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
AUC_{inf}	Area under the plasma concentration versus time curve extrapolated to infinite time
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval
BA	Bioavailability
BCRP	Breast cancer resistance protein
BID	bis in die
BSEP	Bile salt export pump
CL	Clearance
CL/F	Apparent oral clearance
CL_{cr}	Creatinine clearance
C_{max}	Maximum plasma concentration
CV	Coefficient of variation
$E_2$17βG	Estradiol 17-β-D-glucuronide
EC_{50}	50% effective concentration
FAS	Full analysis set
FCV	Famciclovir
HCMV	Human cytomegalovirus
HEF	Human embryonic fibroblast
HEK	Human embryonic kidney
HIV-1	Human immunodeficiency virus type 1
HPLC	High performance liquid chromatography
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
IC_{50}	50% inhibitory concentration
MATE	Multidrug and toxin extrusion
MDCK	Madin-Darby canine kidney
mRNA	Messenger ribonucleic acid
MRP	Multidrug resistance-associated protein
NAG	N-Acetyl-β-D-glucosaminidase
net flux ratio	Ratio of permeability coefficient in transporter-expressing cells to that in the control cells
NTCP	Sodium-taurocholate cotransporting polypeptide
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEPT	Peptide transporter
P-gp	P-glycoprotein
PHN	Post herpetic neuralgia
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QD	quaque die
QTc	Corrected QT interval

QTcF	Fridericia-corrected QT interval
$t_{1/2}$	Elimination half-life
TID	ter in die
Time above 50/100/200/400	Duration of the day in which plasma amenamevir concentration is maintained at ≥50, 100, 200, or 400 ng/mL
t_{max}	Time to maximum plasma concentration
URAT	Urate transporter
VACV	Valaciclovir
Vero	African green monkey kidney cells
VZV	Varicella zoster virus
α1-MG	α1-Microglobulin

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

Once infected through respiratory or ocular mucosa, varicella zoster virus (VZV) proliferates in the lymph nodes, liver, spleen, etc., and approximately 2 weeks after infection, varicella lesion develops. Although varicella spontaneously heals in several weeks, VZV is latently-infected in the ganglia. Latently-infected VZV is reactivated as a consequence of decreased immune function due to overwork, aging, malignant tumor, autoimmune disease, immunosuppressive agent, etc., leading to onset of herpes zoster, of which major symptoms include skin lesion and pain. The skin lesion heals in 2 to 3 weeks after onset, but the pain may persist as post herpetic neuralgia (PHN). PHN is a peripheral neuropathic pain caused by neurodegeneration due to virus infection and may become refractory (*Comprehensive Handbook of Clinical Dermatology 15*. First edition. 2003;33-41, *Handbook of Viral Skin Diseases*. 2011;67-76).

Amenamevir is an antiviral agent discovered by Astellas Pharma Inc. and is considered to exert an antiviral effect by inhibiting the activity of the helicase-primase complex, which is involved in DNA replication of herpes virus.

Outside of Japan, development of amenamevir was implemented by Astellas Pharma Global Development, Inc. and Astellas Pharma Europe B.V. However, [redacted] because serious thrombocytopenia, etc. for which a causal relationship to amenamevir could not be ruled out were observed in a phase I study in the US (Study 15L-CL-019), and the development was suspended in February 2011.

Later, Maruho Co., Ltd, the applicant, acquired a license for the development in and outside of Japan, and then conducted a phase III study in patients with herpes zoster (Study M522101-J01), based on the safety data from non-clinical studies and Japanese clinical studies conducted by Astellas Pharma Inc. The applicant has submitted a marketing application for Amenalief, claiming that the efficacy and safety of amenamevir have been confirmed in patients with herpes zoster.

After the development was suspended outside of Japan in February 2011, a clinical pharmacology study in healthy adult subjects was conducted in Europe, but the development outside of Japan has not been re-started as of now.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as white crystals. The solubility, hygroscopicity, melting point (degradation point), distribution coefficient, and crystalline polymorphism have been determined. [redacted] shows that the drug substance is present in 2 crystal forms, but the manufacturing process on a commercial production scale has been demonstrated to produce the drug substance in 1 crystal form which is thermodynamically stable.

The chemical structure of the drug substance has been elucidated by elementary analysis, mass spectrometry, ultraviolet spectrophotometry, infrared spectrophotometry, and nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR).

2.1.2 Manufacturing process

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

[redacted] are defined as critical steps. [redacted] is defined as a critical intermediate, and control parameters and control values are established.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (ultraviolet-visible spectrophotometry and infrared spectrophotometry), purity (heavy metals, related substances [high-performance liquid chromatography (HPLC)], and residual solvents [gas chromatography]), water content, residue on ignition, [redacted], and assay (HPLC).

2.1.4 Stability of drug substance

Major stability studies conducted on the drug substance are as shown in Table 1. Photostability data show that the drug substance is unstable to light.

Table 1. Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot batches	25 ± 2°C	60 ± 5%RH	Polyethylene bags (double-layered) + aluminum-laminated bag + fiber drum	36 months
	3 commercial batches				12 months
Accelerated testing	3 pilot batches	40 ± 2°C	75 ± 5%RH		6 months
	3 commercial batches				6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored in the double-layered polyethylene bags, which are placed in the aluminum-laminated bag and then further in the fiber drum under light-protected conditions at room temperature. The long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a tablet each containing 200 mg of amenamevir. It contains hypromellose, croscarmellose sodium, crospovidone, [redacted], calcium silicate, magnesium stearate, talc, [redacted], titanium oxide, and [redacted] as excipients.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of coating agent preparation, [redacted], compression, film-coating, packaging, labeling, testing, and storage processes. Of these processes, [redacted] are defined as critical steps, and process control parameters and process control values are established for [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include content, description, identification ([redacted]), purity (related substances [HPLC]), uniformity of dosage units (mass variation), [redacted], dissolution ([redacted]), and assay (HPLC).

2.2.4 Stability of drug product

Major stability studies conducted on the drug product are as shown in Table 2. Photostability data show that the drug product is photostable.

Table 2. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot batches	25 ± 2°C	60 ± 5%RH	PTP (polypropylene film/aluminum foil) package	36 months
Accelerated testing	3 pilot batches	40 ± 2°C	75 ± 5%RH		6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product when stored in a PTP (polypropylene film/aluminum foil) sheet at room temperature. The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and drug product is appropriately controlled.

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

The pharmacological effect of amenamevir was investigated in primary pharmacodynamic and safety pharmacology studies. No secondary pharmacodynamic studies have been conducted.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* antiviral activity

3.1.1.1 Antiviral activity against VZV, HSV-1, and HSV-2 (CTD 4.2.1.1-1 to 4.2.1.1-6)

Antiviral activities of amenamevir and aciclovir (ACV) were investigated in human embryonic fibroblast (HEF) cells or African green monkey kidney cells (Vero) infected with any of the laboratory isolates and Japanese and foreign clinical isolates of VZV, herpes simplex virus (HSV) type1 (HSV-1), and herpes simplex virus type 2 (HSV-2). The results are as shown in Table 3.

Table 3. *In vitro* antiviral activities of amenamevir and ACV against VZV, HSV-1, and HSV-2

Virus strain			Host cells	EC_{50} (μmol/L)	
				Amenamevir	ACV
VZV	Laboratory isolate	CaQu strain	HEF cells	0.10	4.1
	Japanese clinical isolate	Saitou strain	HEF cells	0.065	4.4
		Takahashi strain		0.078	5.9
		Housen strain		0.10	5.2
		Tokumaru strain		0.055	3.0
	US clinical isolate	Hunter strain	HEF cells	0.042	1.3
		Klein strain		0.050	1.6
		Mazzola strain		0.038	1.8
		Negg strain		0.043	1.7
HSV-1	Laboratory isolate	KOS strain	HEF cells	0.037	0.16
		KOS strain	Vero cells	0.027	2.1
		Miyama strain		0.022	1.7
	Japanese clinical isolate	WT-51 strain	HEF cells	0.042	0.15
		WT-51 strain	Vero cells	0.030	0.73
		H-5 strain		0.028	1.4
		Miyoshi strain		0.036	1.5
		Fujito strain		0.029	1.0
		Endo strain		0.023	1.2
	US clinical isolate	CI-25 strain	HEF cells	0.030	0.17
		CI-114 strain		0.018	0.092
		CI-116 strain		0.016	0.080
HSV-2	Laboratory isolate	G strain	HEF cells	0.056	0.41
		Lyon strain		0.12	0.35
		G strain	Vero cells	0.025	1.6
		Lyon strain		0.034	2.6
	Japanese clinical isolate	Kondo strain	HEF cells	0.064	0.20
		Kondo strain	Vero cells	0.023	1.4
	US clinical isolate	CI-27 strain	HEF cells	0.036	0.42
		CI-5243 strain		0.032	0.20

3.1.1.2 Antiviral activities against ACV-resistant VZV and HSV-1 (CTD 4.2.1.1-1, 4.2.1.1-3, 4.2.1.1-4)

Antiviral activities of amenamevir and ACV against ACV-resistant strains were investigated in HEF cells or Vero cells infected with any of the ACV-resistant[1)] laboratory isolates (Kanno-Br strain, A4-3 strain) of VZV and HSV-1. The results are as shown in Table 4.

Table 4. *In vitro* antiviral activities of amenamevir and ACV against ACV-resistant VZV and HSV-1

Virus strain		Host cells	EC_{50} (μmol/L)	
			Amenamevir	ACV
VZV	Kanno-Br strain	HEF cells	0.082	27
HSV-1	A4-3 strain	HEF cells	0.068	120
HSV-1	A4-3 strain	Vero cells	0.026	49

1) In accordance with the article of Saint-Le´ger E, et al. (*Clin Infect Dis.* 2001;33:2061-7), strains of VZV with EC_{50} of ACV ≥ 4-fold EC_{50} (3.0-5.9 μmol/L) against the laboratory isolate (CaQu strain) and Japanese clinical isolates (Saitou strain, Takahashi strain, Housen strain, Tokumaru strain) are defined as ACV-resistant strains of VZV.

3.1.1.3 Antiviral activity of amenamevir metabolite (R5) against VZV, HSV-1, and HSV-2 (CTD 4.2.1.1-12, 4.2.1.1-13)

Antiviral activities of amenamevir and its metabolite (R5) against VZV, HSV-1, and HSV-2 were investigated using human fetal lung fibroblast cells (MRC-5 cells) infected with any of their laboratory isolates (Webster strain, F strain, or MS strain). Results are as shown in Table 5.

Table 5. *In vitro* antiviral activities of amenamevir and its major metabolite (R5) against VZV, HSV-1, and HSV-2

Test strain		Host cells	EC_{50} (μmol/L)	
			Amenamevir	Metabolite (R5)
VZV	Webster strain	MRC-5 cells	0.175	0.762
HSV-1	F strain		0.021	0.258
HSV-2	MS strain		0.040	0.300

3.1.1.4 Antiviral activity against the other viruses (CTD 4.2.1.1-7 to 4.2.1.1-9, Reference CTD 4.2.1.1-10)

The antiviral activity of amenamevir against RS virus, influenza virus, and human cytomegalovirus (HCMV) was investigated, and the 50% effective concentration (EC_{50}) against any virus was determined to be >25 μmol/L. In addition, amenamevir did not affect the cell death rate of human T cells infected with human immunodeficiency virus type 1 (HIV-1) and the amount of HIV-1 p24 antigen in the conditioned medium at the concentration up to 25 μmol/L.

3.1.2 Cytotoxicity against host cells (CTD 4.2.1.1-11)

HEF cells and Vero cells were cultured in the presence of amenamevir for 3 days, and then viable cells were counted using neutral red. The concentration of amenamevir at which the viable cell count was decreased by 50% was >200 μmol/L in either cell line.

3.1.3 Mechanism of action

3.1.3.1 Inhibitory effect against helicase activity of HSV-1 helicase-primase complex (CTD 4.2.1.1-15)

An inhibitory effect of amenamevir against helicase activity of the recombinant HSV-1 helicase-primase complex of wild-type HSV-1 KOS strain was investigated by electrophoresis using the amount of single-stranded DNA synthesized as an indicator. Amenamevir inhibited the helicase activity of the HSV-1 helicase-primase complex at the concentrations ≥0.1 μmol/L.

3.1.3.2 Inhibitory effect against primase activity of HSV-1 helicase-primase complex (CTD 4.2.1.1-16)

An inhibitory effect of amenamevir against primase activity of the recombinant HSV-1 helicase-primase complex of wild-type HSV-1 KOS strain was investigated by electrophoresis using the amount of RNA primer synthesized based on a DNA oligonucleotide template as an indicator. Amenamevir inhibited the primase activity of the HSV-1 helicase-primase complex at the concentrations ≥0.03 μmol/L.

3.1.3.3 Inhibitory effect against DNA-dependent ATPase activity of HSV-1 helicase-primase complex (Reference CTD 4.2.1.1-14)

An inhibitory effect of amenamevir against DNA-dependent ATPase activity of the recombinant HSV-1 helicase-primase complex of wild-type HSV-1 KOS strain was investigated using the amount of inorganic phosphate released by ATP hydrolysis as an indicator. Amenamevir inhibited the DNA-dependent ATPase activity of the HSV-1 helicase-primase complex within the concentration range from 0.0001 to 3 μmol/L in a concentration-dependent manner, and the 50% inhibitory concentration (IC_{50}) was 0.078 μmol/L.

3.1.3.4 Inhibitory effect against DNA replication (CTD 4.2.1.1-17, Reference CTD 4.2.1.1-14)

The inhibitory effects of amenamevir and ACV against DNA replication of VZV were investigated. In this investigation, HEF cells infected with a laboratory isolate (CaQu strain) of VZV were added to amenamevir (0.01-1 μmol/L) or ACV (0.1-10 μmol/L), and the amount of VZV DNA in the cells on Day 3 of infection was determined as an indicator of the inhibitory effect. Amenamevir and ACV

decreased the amount of VZV DNA in the cells in a concentration-dependent manner, and their IC_{50} were 0.057 μmol/L and 0.44 μmol/L, respectively.

The inhibitory effect of amenamevir against DNA replication of VZV, HSV-1, HSV-2, and HCMV was investigated. In this investigation, HEF cells infected with each virus were added to amenamevir (0.003-1 μmol/L), and the amount of virus-specific DNA fragment in the cells was determined as an indicator of the inhibitory effect. Amenamevir inhibited DNA replication of VZV, HSV-1, and HSV-2 at the concentrations of ≥0.03 μmol/L, but did not inhibit that of HCMV even at the highest concentration.

3.1.4 Investigation of development of resistant virus (CTD 4.2.1.1-18 to 4.2.1.1-21)

Development frequency of amenamevir- or ACV-resistant[2)] virus was investigated. In this investigation, Vero cells infected with any of a laboratory isolate (KOS strain) of HSV-1, or laboratory isolates (G strain or Lyon strain) or Japanese clinical isolate (Kondo strain) of HSV-2 were incubated in the presence of amenamevir or ACV at the concentration 20-fold EC_{50} [see Section 3.1.1.1] against the corresponding virus strain, and the count of plaques formed was determined as an indicator of the resistant virus. Results are as shown in Table 6.

Table 6. Development frequency of amenamevir- or ACV-resistant HSV-1 and HSV-2 strains

Virus strain		Amenamevir		ACV	
		Concentration (μmol/L)[a)]	Development frequency of resistant virus[b)]	Concentration (μmol/L)[a)]	Development frequency of resistant virus[b)]
HSV-1	KOS strain	0.52	1.30×10^{-6}	42	0.86×10^{-3}
HSV-2	G strain	0.50	4.17×10^{-6}	32	8.43×10^{-2}
	Lyon strain	0.68	6.67×10^{-6}	52	6.22×10^{-3}
	Kondo strain	0.46	3.51×10^{-6}	28	1.04×10^{-3}

a) Concentration 20-fold EC_{50} against the corresponding virus strain
b) Total plaque count in the presence of the test drug / total plaque count in the absence of the test drug

Vero cells infected with any of a laboratory isolate (KOS strain) or Japanese and foreign clinical isolates (WT-51 strain, CI-25 strain, or CI-116 strain) of HSV-1, or laboratory isolates (G strain or Lyon strain) or Japanese and foreign clinical isolates (Kondo strain or CI-5243 strain) of HSV-2 were incubated in the presence of amenamevir or ACV at the concentration as high as 20-fold EC_{50}[see Section 3.1.1.1] against the corresponding virus strain, and the virus titers from the infection to 168 hours post-infection were determined by the plaque method. In the presence of amenamevir, an increase in virus titer was observed in the cells infected with a clinical isolate (CI-25 strain) of HSV-1 at 120 hours post-infection, but in the cells infected with any of the other virus strains, the virus titer was found to be below the lower detection limit up to 168 hours post-infection. In the presence of ACV, on the other hand, the virus titer increased in the cells infected with any virus strain of HSV-1 and HSV-2 up to 168 hours post-infection.

3.1.5 *In vivo* antiviral activity

3.1.5.1 Suppression of development of skin lesion in a mouse HSV-1 skin infection model (CTD 4.2.1.1-22)

In a mouse skin infection model in which the back skin of mice was infected with a Japanese clinical isolate (WT-51 strain) of HSV-1, amenamevir (0.3, 1, 3, 10, or 30 mg/kg), valaciclovir (VACV) (3, 10, 30, or 100 mg/kg), or placebo (0.5% methylcellulose solution) was orally administered bis in die (BID) for 5 days with the first dose given at 3 hours post-infection, and the suppressive effect against development of skin lesion was investigated until Day 17 post-infection using the skin lesion score (*Antiviral Res.* 1992;17:133-43) as an indicator. Amenamevir and VACV suppressed increases in skin lesion score in a dose-dependent manner, and their 50% effective dose (ED_{50}) were 1.9 mg/kg and 27 mg/kg, respectively.

3.1.5.2 Therapeutic effect on skin lesion in a mouse HSV-1 skin infection model (CTD 4.2.1.1-23)

In a mouse skin infection model in which the back skin of mice was infected with a US clinical isolate (CI-116 strain) of HSV-1, amenamevir (50 mg/kg), VACV (100 mg/kg), or placebo (placebo for

2) Plaques that survived at the concentration as high as 20-fold EC_{50} [see Section 3.1.1.1] of amenamevir or ACV against the corresponding virus strain were defined as the drug-resistant-resistant strains.

amenamevir, a solution containing 25% (w/v) Cremophor EL and 25% (w/v) polyethylene glycol 400; placebo for VACV, 0.5% methylcellulose solution) was orally administered BID for 5 days with the first dose given on Day 3, 4, or 5 post-infection, and the therapeutic effect on the skin lesion was investigated until Day 21 post-infection using the skin lesion score (*Antiviral Res.* 1992;17:133-43) as an indicator. The skin lesion score in mice which started amenamevir on Day 3 or 4 post-infection was lower than that in mice receiving placebo, but the score in mice which started it on Day 5 post-infection was similar to that in mice receiving placebo. The skin lesion score in mice which started VACV on Day 3 post-infection was lower than that in mice receiving placebo, but the score in mice which started it on Day 4 or 5 post-infection was similar to that in mice receiving placebo.

3.1.5.3 Suppression of development of vaginal lesion in a guinea pig HSV-2 vaginal infection model (CTD 4.2.1.1-24)

In a vaginal infection model in which the vagina of guinea pigs was infected with a laboratory isolate (G strain) of HSV-2, amenamevir (0.3, 1, 3, 10, or 30 mg/kg), VACV (30, 100, or 300 mg/kg), or placebo (0.5% methylcellulose solution) was orally administered BID for 5 days with the first dose given at 3 hours post-infection, and the suppressive effect against development of vaginal lesion was investigated until Day 21 post-infection using the vaginal lesion score (*Nat Med.* 2002;8:392-8) as an indicator. Both amenamevir and VACV suppressed increases in vaginal lesion score in a dose-dependent manner, and their ED_{50} were 0.37 mg/kg and 68 mg/kg, respectively.

3.1.5.4 Therapeutic effect on vaginal lesion in a guinea pig HSV-2 vaginal infection model (CTD 4.2.1.1-25)

In a vaginal infection model in which the vagina of guinea pigs was infected with a laboratory isolate (G strain) of HSV-2, amenamevir (1, 3, 10, or 30 mg/kg), VACV (30, 100, or 300 mg/kg), or placebo (0.5% methylcellulose solution) was orally administered BID for 5 days with the first dose given on Day 4 post-infection, and the therapeutic effect on vaginal lesion was investigated until Day 9 post-infection using the vaginal lesion score (*Nat Med.* 2002;8:392-8) as an indicator. Amenamevir suppressed an increase in vaginal lesion score in a dose-dependent manner, and the vaginal lesion scores at the doses of 3, 10, and 30 mg/kg were smaller than that for placebo. VACV suppressed an increase in vaginal lesion score only at the dose of 300 mg/kg.

3.1.5.5 Reducing effect on intravaginal HSV-2 virus titer in a guinea pig HSV-2 vaginal infection model (CTD 4.2.1.1-26)

In a vaginal infection model in which the vagina of guinea pigs was infected with a laboratory isolate (G strain) of HSV-2, amenamevir (10 or 30 mg/kg), VACV (300 mg/kg), or placebo (0.5% methylcellulose solution) was orally administered BID on Day 4 post-infection, and the intravaginal HSV-2 virus titer was determined on the following day of the test drug administration by the plaque method. The virus titers in the amenamevir (10 and 30 mg/kg) group were lower than that in the placebo group, but that in the VACV (300 mg/kg) group was similar to that in the placebo group.

3.1.6 PK/PD analysis of amenamevir in a mouse HSV-1 skin infection model (CTD 4.2.1.1-27, 4.2.1.1-28)

In a skin infection model in which the back skin of mice was infected with a Japanese clinical isolate (WT51 strain) of HSV-1, amenamevir 1 to 100 mg/kg/day was orally administered once, twice, or 3 times a day for 5 days with the first dose given at 2 to 3 hours post-infection, and the intradermal HSV-1 virus titer was determined on Day 5 post-infection by the plaque method. From changes in plasma amenamevir concentration over time, pharmacokinetics (PK)/pharmacodynamics (PD) parameters related to the intradermal virus titer were estimated. The results showed that the virus titer was reduced corresponding to the daily dose of amenamevir; amenamevir 30 mg/kg/day in 3 divided doses and 100 mg/kg/day in 2 divided doses reduced the virus titer to almost the lower detection limit (2.4 $\log_{10}$ pfu/skin). In addition, with respect to the antiviral effect of amenamevir, a certain correlation was observed between the HSV-1 virus titer and AUC_{24h} and between the titer in question and duration of the day in which the plasma concentration was maintained at >100 ng/mL (Time above 100) (R^2 = 0.9005 and 0.8227, respectively).

3.2 Safety pharmacology (CTD 4.2.1.3-1 to 4.2.1.3-4)

Effects of amenamevir on the central nervous, cardiovascular, and respiratory systems were investigated (Table 7).

Table 7. Summary of safety pharmacology studies

Organs to be evaluated	Test system	Endpoint, method, etc.	Dose or concentration	Route of administration	Special findings
Central nervous system	ICR mice (6 males/group)	Irwin method	0, 10, 50, 250 mg/kg	Oral	None
Cardiovascular system	HEK-293 cells (5 specimens/ concentration)	hERG current	0, 0.3, 3, 30 μmol/L	*in vitro*	Inhibited by 18.6% at 30 μmol/L
	Isolated Hartley guinea pig papillary muscle (5 specimens from females/concentration)	Myocardial action potential	0, 0.3, 3, 30 μmol/L	*in vitro*	Action potential durations at 30%, 60%, and 90% repolarization prolonged by 6.2%, 4.7%, and 3.9% at 30 μmol/L
	Beagle dogs (4 males/group)	Telemetry method	0, 10, 50, 250 mg/kg	Oral	None
Respiratory system	Beagle dogs (4 males/group)	Telemetry method	0, 10, 50, 250 mg/kg	Oral	None

The applicant's explanation on effects of amenamevir on the cardiac conduction system:
Amenamevir inhibited hERG current at 30 μmol/L (14.5 μg/mL). In addition, an investigation using isolated Hartley guinea pig papillary muscles showed that amenamevir prolonged the action potential duration at repolarization by 3.9% to 6.2% at 30 μmol/L (14.5 μg/mL), but a difference in action potential duration between 30% and 90% repolarization was as minimal as −0.4%. Amenamevir is, therefore, considered to have no effect on delayed rectifier potassium channel current. In addition, a telemetry study in dogs showed that amenamevir transiently decreased blood potassium concentration at 3 hours after administration at ≥50 mg/kg, but the QT interval was not prolonged at the doses up to 250 mg/kg. The maximum plasma concentration (C_{max}) in dogs following administration of amenamevir 250 mg/kg was 24.2 μg/mL, which was approximately 10-fold the human exposure following administration of amenamevir 400 mg (C_{max} 1.94 μg/mL [see Section 6.2.2.1]).

Based on the above, amenamevir is considered unlikely to affect the cardiovascular system in routine clinical use.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of amenamevir against VZV and antiviral activity

The applicant's explanation on antiviral activities of amenamevir and ACV against recent clinical isolates of VZV:
Antiviral activities of amenamevir and ACV were investigated using HEF cells infected with clinical isolates (46 strains) of VZV obtained from patients with herpes zoster enrolled in a phase III study (Study M522101-J01). The results showed that IC_{50} of amenamevir and ACV against each clinical isolate of VZV was 0.08 to 0.49 μmol/L and 0.78 to 2.8 μmol/L, respectively, indicating that amenamevir has higher antiviral activity than ACV.

The mechanism of action and *in vivo* antiviral activity of amenamevir have been investigated using HSV-1, but the applicant explained the mechanism of action and *in vivo* antiviral activity against VZV. PMDA therefore asked the applicant to explain the rationale why they considered it possible to explain these properties against VZV based on the study data against HSV-1.

The applicant's explanation:
Investigation for the mechanism of action suggested that amenamevir inhibits helicase activity, primase activity, and DNA-dependent ATPase activity of the helicase-primase complex, which is essential for DNA replication of HSV-1 [see Section 3.1.3]. The helicase-primase complex of HSV-1 consists of 3 subunits, UL5, UL52, and UL8, of which the UL5 subunit has the helicase activity and DNA-dependent ATPase activity, and the UL52 subunit has the primase activity (*Annu Rev Biochem.* 1997;66:347-84, *Nat Med.* 2002;8:327-8, *Nucleic Acids Res.* 1990;18:3573-8). In addition, in amenamevir-resistant strains of HSV-1 obtained through passage culture in the presence of amenamevir, amino acid substitutions were observed in UL5 and UL52, suggesting that action target of amenamevir against HSV-1 is the helicase-primase complex (*Biochem Pharmacol.* 2012;84:459-67).

Gene clusters of the helicase-primase complex are highly homologous among viruses (including HSV-1 and VZV) under the α herpes virus subfamily; the helicase-primase complex of VZV consists of ORF55, ORF6, and ORF52, which are orthologs of UL5, UL52, and UL8 of HSV-1, respectively (*J Virol*. 2013;87:6943-54). In addition, in amenamevir-resistant strains of VZV obtained through passage culture in the presence of amenamevir, amino acid substitutions were observed in ORF55 and ORF6 (*J Antimicrob Chemother.* 2010;65:1733-41). Based on the above, the action target of amenamevir against VZV is the helicase-primase complex as with HSV-1.

In addition, to investigate *in vivo* antiviral activity of amenamevir against VZV, the skin infection model mice of HSV-1, which belongs to the same α herpes virus subfamily as that of VZV, were used, because VZV has high species specificity, and thus an animal model presenting with herpes zoster has not been established. In skin infection model mice of HSV-1, blisters develop along with ganglions following the initial infection, consequently forming skin lesion similar to herpes zoster in humans. The investigation using this model suggested effects of amenamevir on the skin lesion [see Section 3.1.5]. As described above, amenamevir is considered to exert the antiviral activity against HSV-1 and VZV through a similar mechanism of action. The applicant therefore considers it possible to explain the *in vivo* antiviral activity of amenamevir against VZV based on the study data from this model.

PMDA's view:
The mechanism of action of amenamevir against VZV should be investigated using VZV, a pathogenic virus of herpes zoster, which is the proposed indication. It, however, was possible to infer that the action target of amenamevir against VZV is the helicase-primase complex leading to inhibition of the activity, based on the submitted study data, because gene clusters of the helicase-primase complex are highly homologous among virus species under the α herpes virus subfamily including HSV and VZV; and the antiviral activity of amenamevir against VZV has been demonstrated *in vitro*. Based on the above, the antiviral activity of amenamevir against VZV is expected.

3.R.2 Development of amenamevir-resistant VZV

PMDA asked the applicant to explain a concern about development of amenamevir-resistant VZV.

The applicant's explanation:
Results from *in vitro* studies for sensitivity to amenamevir using HSV-1 and HSV-2 showed that the development frequency of virus resistant to amenamevir was lower than that to ACV [see Section 3.1.4]. In addition, in amenamevir-resistant strains of HSV obtained through passage culture in the presence of amenamevir, amino acid substitutions were observed in the helicase-primase complex, which is the action target of amenamevir and is essential for DNA replication in all α herpes virus subfamily, and the proliferation rates of these mutant strains were lower than that of the wild-type strain (*Biochem Pharmacol*. 2012;84:459-67). Similarly, amino acid substitutions were observed in the helicase-primase complex of amenamevir-resistant strains of VZV obtained through passage culture in the presence of amenamevir, and the proliferation rates of these mutant strains were lower than that of the wild-type strain (*J Antimicrob Chemother.* 2010;65:1733-41). In addition, because the proliferation rate of VZV is lower than that of HSV (*Antibiotics & Chemotherapy.* 2015;31:46-54), development frequency of DNA point mutation in gene clusters coding helicase and primase of VZV is inferred to be lower than that of HSV.

Based on the above, the applicant considers that the concern about development of VZV resistant to amenamevir is lower than that to ACV.

PMDA's view on development of amenamevir-resistant VZV:
The applicant explained that a concern about development of VZV resistant to amenamevir is lower than that to ACV at present, based on the presented information that amenamevir is shown to have higher antiviral activity against HSV and VZV than ACV [see Section 3.1.1.1]; in the investigation using HSV, the development frequency of virus resistant to amenamevir is lower than that to ACV [see Section 3.1.4]; and the action target of amenamevir against both HSV and VZV is the helicase-primase complex. In this regard, the applicant's explanation is acceptable. Passage culture of VZV in the presence of amenamevir, however, actually led to development of amenamevir-resistant strains, and therefore the applicant is required to continue collecting information on development of resistance to amenamevir

even after the market launch and, when new findings become available, to provide the information to healthcare professionals.

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

Amenamevir or ^{14}C- amenamevir was intravenously or orally administered to mice, rats, and dogs under fasted or fed conditions to evaluate the PK. Concentrations of amenamevir or its metabolites in plasma or biological samples were measured by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) (lower limit of quantitation of amenamevir, 5 ng/mL in plasma and 0.5 μg/mL in urine; lower limit of quantitation of its metabolite [R5], 6 ng/mL in plasma). The radioactivity concentrations in biological samples were measured using a liquid scintillation counting method.

Unless otherwise specified, PK parameters are expressed as the mean.

4.1 Absorption

4.1.1 Single-dose administration (CTD 4.2.2.2-1, 4.2.2.2-2, 4.2.2.2-4, 4.2.2.2-6, 4.2.2.2-7)

Table 8 shows pharmacokinetic parameters of amenamevir in plasma following a single oral dose of and a single intravenous dose of amenamevir in mice and dogs. The exposure was almost dose-proportional within dose ranges from 1 to 10 mg/kg in mice and from 0.3 to 3 mg/kg in dogs.

Table 8. PK parameters of amenamevir following a single oral dose of or a single intravenous dose of amenamevir

Animal species	Route of administration	Dose (mg/kg)	No. of animals	C_{max} (μg/mL)	t_{max} (h)	AUC_{inf} (μg·h/mL)	CL (L/h/kg)	V_d (L/kg)	$t_{1/2}$ (h)	F (%)
Mouse	Oral	1	3 males/ timepoint	0.07	1.0	0.35	-	-	-	40.5
		3	3 males/ timepoint	0.26	1.0	1.05	-	-	-	40.5
		10	3 males/ timepoint	0.89	1.0	3.97	-	-	-	46.1
	Intravenous	3	3 males/ timepoint	-	-	2.59	1.16	3.14	2.3	-
Dog	Oral	0.3	4	0.03 ± 0.01	2.5 ± 1.0	0.51 ± 0.16	-	-	8.8 ± 1.4	21.9 ± 7.32
		1	4	0.10 ± 0.01	3.5 ± 1.0	1.76 ± 0.29	-	-	9.2 ± 1.0	23.1 ± 6.73
		3	4	0.45 ± 0.18	3.5 ± 1.0	7.87 ± 3.28	-	-	8.6 ± 1.1	33.1 ± 11.0
	Intravenous	1	4	-	-	7.87 ± 1.35	0.13 ± 0.02	1.74 ± 0.05	9.7 ± 1.5	-

Mean ± standard deviation (SD)
-, Not investigated

Table 9 shows pharmacokinetic parameters of radioactivity in plasma or blood following a single oral dose of and a single intravenous dose of ^{14}C-amenamevir in mice, rats, and dogs.

Table 9. PK parameters of radioactivity following a single oral dose of and a single intravenous dose of ^{14}C-amenamevir

Animal species	Route of administration	Dose (mg/kg)	Specimens	No. of animals	C_{max} (μg eq./L)	t_{max} (h)	AUC_{inf} (μg eq.·h/L)	$t_{1/2}$ (h)	F (%)
Mouse	Oral	3	Blood	3 males/ timepoint	0.36	1.0	1.61	5.2	38.8
			Plasma	3 males/ timepoint	0.43	1.0	1.82	2.5	40.1
	Intravenous	3	Blood	3 males/ timepoint	1.89	-	4.14	6.7	-
			Plasma	3 males/ timepoint	2.39	-	4.55	3.2	-
Rat	Oral	3	Plasma	3 males/ timepoint	0.12	1.0	0.52	1.5	-
Dog	Oral	1	Blood	3 males	0.21 ± 0.06	2.7 ± 1.2	5.14 ± 1.82	87 ± 48	-
			Plasma	3 males	0.21 ± 0.08	3.3 ± 1.2	4.18 ± 2.19	16 ± 2	-

Mean ± SD
-, Not investigated

^{14}C-amenamevir 0.03 mg/loop was injected into the loop of mice with a gastrointestinal loop (n = 3 males/group). The absorption rates at 1 hour after injection in the stomach, upper small intestine, middle

small intestine, lower small intestine, and large intestine were 4.36%, 32.1%, 21.3%, 16.5%, and −0.17%, respectively.

4.1.2 Repeated-dose administration (CTD 4.2.2.2-3, 4.2.2.2-5, 4.2.3.7.7-6)

Table 10 shows pharmacokinetic parameters of amenamevir and its major metabolites (R5) in plasma following repeated oral administration of amenamevir in mice, rats, and dogs. The plasma amenamevir concentration decreased following repeated administration. In addition, C_{max} and $AUC_{0\text{-}24}$ of amenamevir and R5 were almost dose-proportional within a dose range up to 60 or 125 mg/kg. The applicant explained that the decrease in amenamevir concentration following repeated administration was possibly caused by autoinduction of hepatic drug-metabolizing enzymes.

Table 10. PK parameters of amenamevir and its metabolite (R5) following repeated oral administration of amenamevir

Amenamevir									
Animal species	Daily dose (mg/kg)	No. of animals	Date of measurement	C_{max} (μg/mL)		t_{max} [a] (h)		$AUC_{0\text{-}24}$ (μg·h/mL)	
				Male	Female	Male	Female	Male	Female
Mouse	60	3/sex/ timepoint	1	18.4	13.5	1.0	0.5	57.9	36.4
			28	18.3	17.8	0.5	0.5	53.2	43.0
	125	3/sex/ timepoint	1	34.6	31.0	0.5	0.5	132	91.9
			28	35.3	32.9	0.5	0.5	104	94.1
	250	3/sex/ timepoint	1	48.7	45.3	2.0	1.0	230	187
			28	45.9	45.4	0.5	0.5	144	144
Rat	60	3/sex/ timepoint	1	7.77	15.0	0.5	2.0	20.5	99.9
			28	8.38	12.2	0.5	0.5	31.3	80.3
	125	3/sex/ timepoint	1	13.4	24.9	0.5	2.0	48.6	188
			28	15.8	22.0	1.0	1.0	64.8	124
	250	3/sex/ timepoint	1	17.0	29.3	1.0	2.0	83.1	262
			28	16.9	23.8	2.0	1.0	80.9	169
Dog	3	3/sex	1	1.35 ± 0.10	1.21 ± 0.05	2.0 [2.0, 2.0]	2.0 [2.0, 2.0]	18.1 ± 0.69	16.1 ± 0.76
			28	1.49 ± 0.04	1.28 ± 0.14	1.0 [1.0, 1.0]	2.0 [0.5, 2.0]	19.5 ± 1.14	17.5 ± 0.83
	10	3/sex	1	4.43 ± 0.36	4.37 ± 0.25	2.0 [1.0, 2.0]	2.0 [1.0, 2.0]	60.5 ± 3.80	60.8 ± 2.85
			28	4.22 ± 0.46	4.07 ± 0.41	1.0 [1.0, 2.0]	2.0 [2.0, 2.0]	55.8 ± 8.32	56.5 ± 6.57
	60	3/sex	1	22.6 ± 1.97	17.9 ± 4.29	4.0 [2.0, 4.0]	4.0 [2.0, 4.0]	370 ± 40.0	282 ± 71.6
			28	20.2 ± 2.75	17.8 ± 0.63	1.0 [1.0, 1.0]	2.0 [1.0, 2.0]	273 ± 25.6	245 ± 16.0
	250	5/sex	1	27.4 ± 5.76	30.4 ± 10.0	4.0 [2.0, 4.0]	4.0 [4.0, 4.0]	425 ± 96.9	495 ± 150
			28	23.3 ± 6.53	23.8 ± 5.71	2.0 [1.0, 4.0]	2.0 [1.0, 4.0]	329 ± 84.6	343 ± 105
R5									
Animal species	Daily dose (mg/kg)	No. of animals	Date of measurement	C_{max} (μg/mL)		t_{max} [a] (h)		$AUC_{0\text{-}24}$ (μg·h/mL)	
				Male	Female	Male	Female	Male	Female
Mouse	60	3/sex/ timepoint	1	1.99	2.15	1.0	2.0	7.34	7.06
			28	2.45	3.06	1.0	1.0	9.11	8.60
	125	3/sex/ timepoint	1	4.44	5.52	2.0	2.0	19.3	18.2
			28	6.61	7.63	1.0	1.0	24.0	22.6
	250	3/sex/ timepoint	1	6.46	7.34	2.0	2.0	34.7	34.9
			28	11.9	10.7	2.0	2.0	44.3	40.8
Rat	60	3/sex/ timepoint	1	1.77	0.30	0.5	1.0	6.00	1.71
			28	1.23	0.30	0.5	0.5	5.20	1.33
	125	3/sex/ timepoint	1	2.94	0.58	2.0	2.0	12.7	3.94
			28	2.55	0.79	1.0	1.0	10.4	3.40
	250	3/sex/ timepoint	1	4.34	0.84	2.0	4.0	20.2	7.01
			28	3.02	1.00	1.0	1.0	13.8	5.71
Dog	3	3/sex	1	0.005 ± 0.005	0.005 ± 0.009	1.0, 1.0 [b]	4.0 [c]	0.017 ± 0.026	0.026 ± 0.044
			28	0.006 ± 0.006	0.009 ± 0.003	1.0, 1.0 [b]	4.0[0.5, 4.0]	0.033 ± 0.030	0.029 ± 0.031
	10	3/sex	1	0.035 ± 0.016	0.039 ± 0.009	2.0 [1.0, 2.0]	2.0 [2.0, 4.0]	0.31 ± 0.19	0.45 ± 0.10
			28	0.039 ± 0.020	0.052 ± 0.009	2.0 [0.5, 2.0]	4.0 [2.0, 4.0]	0.32 ± 0.18	0.58 ± 0.09
	60	3/sex	1	0.41 ± 0.23	0.27 ± 0.10	8.0 [4.0, 8.0]	4.0 [4.0, 4.0]	6.99 ± 4.53	3.40 ± 1.43
			28	0.74 ± 0.46	0.41 ± 0.09	2.0 [1.0, 4.0]	4.0 [1.0, 4.0]	7.82 ± 4.68	4.04 ± 0.48
	250	5/sex	1	0.38 ± 0.13	0.46 ± 0.20	4.0 [4.0, 4.0]	4.0 [4.0, 8.0]	4.82 ± 1.77	7.00 ± 3.79
			28	0.56 ± 0.18	0.67 ± 0.36	4.0 [4.0, 4.0]	4.0 [4.0, 4.0]	5.22 ± 1.53	8.42 ± 4.90

Mean ± SD

a) Median (range), b) Individual values from 2 animals, c) Value from 1 animal

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.2-2, 4.2.2.3-1 to 4.2.2.3-3)

Following a single oral dose of 3 mg/kg of ^{14}C-amenamevir in albino mice (3 males/timepoint) and pigmented mice (3 males/timepoint), tissue distribution of radioactivity was investigated. In albino mice,

the radioactivity concentration reached the maximum at 1 hour post-dose in many tissues, and the concentration was highest in the liver, followed in descending order by the small intestine, Harderian gland, kidney, and large intestine. Up to 24 hours post-dose, the concentration decreased to below the lower limit of quantitation in all the tissues except for the liver, Harderian gland, blood, stomach, kidney, heart, and lung. Concerning distribution in melanin containing tissues, elimination of the radioactivity from the eye was slower than that from the other tissues in pigmented mice, but the radioactivity concentration decreased to below the lower limit of quantitation at 672 hours post-dose. Based on the above result, the applicant explained that binding of amenamevir to melanin-containing tissues is considered to be reversible.

Tissue distribution of radioactivity was investigated following repeated oral administration of ^{14}C-amenamevir 3 mg/kg/day in albino mice (3 males/timepoint) for 21 days. Radioactivity in each tissue reached the steady state 7 days after the administration, and was eliminated up to 24 or 168 hours after end of administration.

Tissue distribution of radioactivity was investigated following a single oral dose of ^{14}C-amenamevir 1 mg/kg in dogs (1 male/timepoint). In all the tissues investigated,[3)] the radioactivity concentration reached the maximum at 4 hours post-dose, and the concentration was highest in the large intestine followed in descending order by the small intestine, liver, kidney, and pancreas. Although the radioactivity concentration in the tissues decreased with time, the radioactivity was detected in all the tissues except for the cerebrum, cerebellum, and tear fluid even at 72 hours post-dose.

4.2.2 Plasma protein binding and distribution into red blood cells (CTD 4.2.2.2-2, 4.2.2.2-7, 4.2.2.3-4 to 4.2.2.3-6)

Amenamevir (50-5000 ng/mL) was added to plasma samples from mice, rats, guinea pigs, rabbits, dogs, and humans. The plasma protein binding was 75.3% to 77.3%, 70.4% to 71.7%, 64.1% to 68.3%, 82.9% to 83.9%, 72.6% to 73.7%, and 75.0% to 75.3%, respectively; the values were similar irrespective of the concentration.

^{14}C-amenamevir (50-5000 ng/mL) was added to human serum protein. The protein binding to human serum albumin, alpha 1-acid glycoprotein, γ-globulin, high-density lipoprotein (HDL), or low-density lipoprotein (LDL) was 42.9% to 44.0%, 6.6% to 7.5%, 4.2% to 5.8%, 22.1% to 24.1%, and 15.7% to 18.6%, respectively.

^{14}C-amenamevir (50-5000 ng/mL) was added to blood samples from mice, rats, rabbits, dogs, and humans. The distribution rates into blood cells were 46.9% to 48.9%, 43.3% to 51.9%, 39.3% to 40.9%, 52.2% to 55.1%, and 46.7% to 49.5%, respectively.

Following a single dose of ^{14}C-amenamevir (3 mg/kg in mice, 1 mg/kg in dogs) in mice (3 males/timepoint) or dogs (3 males) (orally or intravenously to mice, orally to dogs), the distribution rates into blood cells were 30.2% to 87.1% (intravenous) and 20.9% to 54.3% (oral) in mice, and 41.0% to 72.9% in dogs.

4.2.3 Transfer into placenta and fetuses (CTD 4.2.2.3-7)

Following a single oral dose of ^{14}C-amenamevir 3 mg/kg in mice on Gestation Day 12 (n = 3/timepoint), tissue distribution of radioactivity was investigated. Ratios of the radioactivity concentrations in the placenta and fetuses to the plasma concentration in maternal animals at 0.5 to 4 hours post-dose were 1.64 to 6.80 and 0.56 to 1.40, respectively.

Following a single oral dose of ^{14}C-amenamevir 3 mg/kg in mice on Gestation Day 16 (n = 1/timepoint), tissue distribution of radioactivity was investigated using wholebody autoradiography. The radioactivity was distributed in many tissues in maternal animals as well as fetuses and fetal liver. The concentration reached the maximum in the placenta, fetuses, and fetal liver at 1 hour post-dose, and then decreased with time.

[3)] Plasma, blood, cerebrum, cerebellum, spinal cord, dorsal root ganglion, pituitary gland, tear fluid, eyeball, trigeminal ganglion, thyroid, heart, lung, liver, kidney, adrenal gland, spleen, pancreas, stomach, small intestine, large intestine, skin, sciatic nerve, bone marrow

Based on the above, amenamevir was suggested to cross through the placenta and transfer into the fetuses.

4.3 Metabolism

4.3.1 Possible metabolic pathways

Investigation results in 4.3.3 *In vivo* metabolism indicated the possible major metabolic pathway of amenamevir as shown in Figure 1. Metabolites[4)] are mainly formed by hydroxylation, amidino-modification, formylation, and glucuronidation, but no human-specific metabolites were detected.

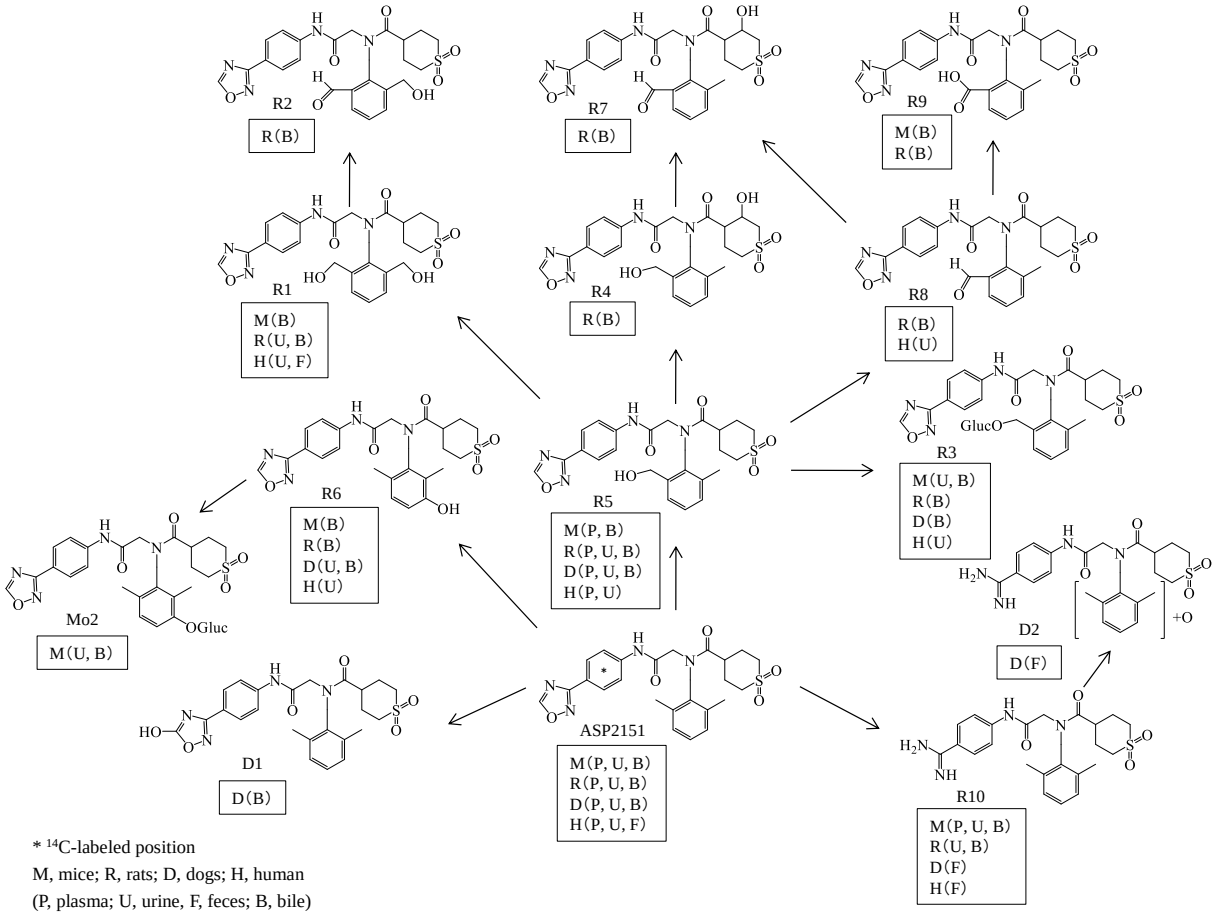

Figure 1. Possible metabolic pathway of amenamevir (from Figure 2.6.4-17, CTD 2.6.4.5.2.1)

4.3.2 *In vitro* metabolism (CTD 4.2.2.4-1 to 4.2.2.4-4)

^{14}C-amenamevir (10 μmol/L) was added to liver microsomes specimens and hepatocytes from mice, rats, rabbits, dogs, and humans. The major metabolite was R5 in any animal species or in any sample, and no human-specific metabolites were detected.

Correlations of the metabolic activity of amenamevir with specific activities of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11) were investigated following addition of amenamevir (20 ng/mL) to human liver microsomes. The results suggested that amenamevir is mainly metabolized by CYP3A4/5, and CYP2B6 and CYP 2C19 are also involved in the metabolism.

Amenamevir (1-100 μmol/L) was added to human liver microsomes to investigate CYP isoforms (CYP2B6, CYP 2C8, CYP 3A4/5) involved in formation of R5. The results suggested that CYP3A4/5 is involved in formation of R5. Furthermore, amenamevir (10 μmol/L) was added to human CYP isoform expression system microsomes. Formation of R5 was only found in the CYP3A4 isoform

4) Major metabolites are as follows:
Hydroxylated metabolites, R1, R4, R5, R6; formylated metabolites, R2, R7, R8; glucuronate conjugates, R3; carboxylate substitution product, R9; amidino-modified metabolite, R10

expression system and was not found in the CYP isoform expression systems (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1).

4.3.3 *In vivo* metabolism (CTD 4.2.2.4-5 to 4.2.2.4-9)

Following a single oral dose of ^{14}C-amenamevir 3 mg/kg in mice and rats (plasma samples collected from 3 males/timepoint, urine and bile samples collected from 4 males), the metabolites in plasma, urine, and bile were investigated. In mice, R5 and R10 were mainly found in plasma in addition to unchanged amenamevir; unchanged amenamevir, R3, Mo2, and R10 were found in urine; and unchanged amenamevir, R1, R3, Mo2, R5, R6, R9, and R10 were found in bile. In rats, unchanged amenamevir and R5 were mainly found in plasma; unchanged amenamevir, R1, R5, and R10 in urine; and unchanged amenamevir, and R1 to R10 in bile.

Following a single oral dose of ^{14}C-amenamevir 1 mg/kg in dogs (3 males/timepoint), the metabolites in plasma, urine, bile, and feces were investigated. Small amounts of R5 and unknown metabolites were found in plasma in addition to unchanged amenamevir, the major compound; unchanged amenamevir, R5, R6, and unknown metabolites were found in urine; and unchanged amenamevir, R3, and monoxide of amenamevir in bile; and R10 and monoxide of R10 in feces. Up to 72 hours post-dose, 7.0%, 19.1%, and 84.8% of the administered radioactivity were excreted into urine, bile, and feces, respectively. The applicant explained that amenamevir is suggested to be degraded by enteric bacteria, because composition of the metabolites in feces was different from that in bile, and in dogs which orally received amenamevir, no unchanged amenamevir was found in feces despite the finding that a certain amount of amenamevir was not absorbed.

The metabolites in plasma, urine, and feces collected from healthy subjects (n = 6) in a clinical study (Study 15L-CL-007) [see Section 6.2.1.5] were investigated. As a result, unchanged amenamevir and R5 were found in plasma; unchanged amenamevir, R1, R5, R6, and unknown metabolites in urine; and unchanged amenamevir, R1, R5, and unknown metabolites in feces.

4.4 Excretion

4.4.1 Excretion into urine, feces, and bile (CTD 4.2.2.2-2, 4.2.2.2-4, 4.2.2.2-6, 4.2.2.2-7)

Following a single oral dose of ^{14}C-amenamevir (3 mg/kg in mice, 1 mg/kg in dogs) in mice (4 males) and dogs (3 males), radioactivity excretion rates into urine and feces (up to 96 hours post-dose in mice, up to 168 hours post-dose in dogs) were 10.1% and 90.5%, respectively, in mice and 7.7% and 87.6%, respectively, in dogs.

Following a single oral dose of ^{14}C-amenamevir (3 mg/kg in mice and rats, 1 mg/kg in dogs) in bile duct-cannulated mice (4 males), rats (4 males), and dogs (3 males), radioactivity excretion rates into urine and bile (urine, bile, and feces only in dogs) (up to 48 hours post-dose in mice, up to 72 hours post-dose in rats and dogs) were 11.79% and 32.04%, respectively, in mice, 2.77% and 26.3%, respectively, in rats, and 13.8%, 19.1%, and 55.6%, respectively, in dogs.

In addition, bile collected from bile duct-cannulated mice which previously received a single oral dose of ^{14}C-amenamevir 3 mg/kg was intraduodenally administered into the other bile duct-cannulated mice. As a result, radioactivity excretion rates into urine and bile at 48 hours post-dose were 4.22% and 17.9%, respectively. The applicant explained that the above result suggested reabsorption of a part of administered amenamevir through enterohepatic circulation.

4.4.2 Excretion into milk (CTD 4.2.2.3-7)

Following a single oral dose of ^{14}C-amenamevir 3 mg/kg to mice on Lactation Day 10 (n = 3/timepoint), the radioactivity concentration in milk reached the maximum (573 ng eq./g) at 1 hour post-dose, and then decreased with time. The ratios of radioactivity concentrations in milk from 0.5 to 24 hours post-dose to those in plasma ranged from 0.712 to 1.18.

4.5 Pharmacokinetic drug interactions

4.5.1 Enzyme induction and inhibition (CTD 4.2.2.6-1 to 4.2.2.6-4)

An induction effect of amenamevir (2-200 µmol/L for induction effect on CYP2B6, 1-100 µmol/L for induction effect on the other CYP isoforms) on CYP isoforms (CYP1A2, CYP2B6, CYP2C9, CYP2C19,

and CYP3A4) was investigated using human hepatocytes. As a result, messenger ribonucleic acid (mRNA) level and enzyme activity of CYP2B6, CYP2C9, CYP2C19, and CYP3A4 increased, suggesting the induction effect of amenamevir. On CYP1A2, on the other hand, no induction effect was presented.

An inhibitory effect of amenamevir (0.1-100 μmol/L) against CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) was investigated using human liver microsomes. Amenamevir inhibited metabolism of amodiaquine, a substrate of CYP2C8, with the IC_{50} value of 69 μmol/L, but no time-dependent inhibitory effect was observed. No clear inhibitory effect was observed against the other CYP isoforms investigated. In addition, an inhibition pattern and Ki value of amenamevir against metabolism of amodiaquine, a substrate of CYP2C8, were investigated using human liver microsomes. As a result, amenamevir inhibited CYP2C8 in a mixed pattern with the Ki value of 32 μmol/L.

4.5.2 Property as a substrate of drug transporters (CTD 4.2.2.6-5, 4.2.2.6-7, 4.2.2.6-8, 4.2.2.6-10)

Transcellular transportation of amenamevir was investigated using porcine renal epithelial cells, LLC-PK1 cells, that expressed human P-glycoprotein (P-gp). The net flux ratio (ratio of permeability coefficient in transporter-expressing cells to that in the control cells) at amenamevir 2.5 μmol/L was 10.8. When either of verapamil and ketoconazole, which inhibits P-gp, was added, the concerned ratio decreased to 1.3 and 1.2, respectively, suggesting that amenamevir is a substrate of P-gp.

Transportation or uptake of amenamevir in various transporter-expressing cells was investigated using human breast cancer resistance protein (BCRP)-expressing Madin-Darby canine kidney (MDCK) cells, human organic anion transporting polypeptide (OATP)1B1, OATP1B3, or organic cation transporter (OCT)2-expressing human embryonic kidney (HEK)293 cells, human organic anion transporter (OAT)1 or OAT3-expressing mouse proximal renal tubule-derived S2 cells, and human multidrug and toxin extrusion (MATE)1 or MATE2-K-expressing HEK293 cells. The results suggested that amenamevir is not a substrate of any of the transporters investigated.

Uptake of amenamevir was investigated using vesicles prepared from human multidrug resistance-associated protein (MRP)2-expressing insect Sf9 cells. As a result, no difference was observed between ATP-dependent and AMP-dependent uptakes of amenamevir, suggesting that this drug is not a substrate of MRP2.

Uptake of amenamevir was investigated using human bile salt export pump (BSEP)-expressing vesicles. As a result, no BSEP-mediated uptake of amenamevir was observed, suggesting that this drug is not a substrate of BSEP.

4.5.3 Inhibitory effect against drug transporters (CTD 4.2.2.6-6, 4.2.2.6-7, 4.2.2.6-9, 4.2.2.6-11)

An inhibitory effect of amenamevir (16 and 200 μmol/L) against P-gp was investigated using human P-gp-expressing MDCKII cells. As a result, amenamevir did not inhibit transportation of vinblastine, a substrate of P-gp; no inhibitory effect of amenamevir against P-gp was presented.

An inhibitory effect of amenamevir (1-200 μmol/L) against BCRP was investigated using human BCRP-expressing MDCK cells. As a result, amenamevir inhibited transportation of prazosin, a substrate of BCRP, suggesting the inhibitory effect of amenamevir against BCRP (IC_{50} value, 94.6 μmol/L).

An inhibitory effect of amenamevir (1-100 μmol/L) against MRP2 was investigated using vesicles prepared from human MRP2-expressing insect Sf9 cells. As a result, amenamevir did not inhibit transportation of estradiol 17-β-D-glucuronide ($E_2$17βG), a substrate of MRP2; no inhibitory effect of amenamevir against MRP2 was presented.

An inhibitory effect of amenamevir against transportation of taurocholic acid was investigated using human BSEP-expressing vesicles in the presence or absence of amenamevir. As a result, amenamevir

(1-100 μmol/L) did not inhibit transportation of taurocholic acid, a substrate of BSEP; no inhibitory effect of amenamevir against BSEP was presented.

An inhibitory effect of amenamevir (1-200 μmol/L) against MATE1 and MATE2-K was investigated using human MATE1 and MATE2-K-expressing HEK293 cells. As a result, amenamevir inhibited intracellular uptake of metformin, a substrate of MATE1 and MATE2-K, suggesting the inhibitory effect of amenamevir against MATE1 and MATE2-K (IC_{50} values; 39.1 and 47.0 μmol/L, respectively).

An inhibitory effect of amenamevir (1-100 μmol/L) against substrates of human peptide transporter (PEPT)1, PEPT2, and urate transporter (URAT)1 was investigated using human PEPT1 or PEPT2-expressing CHO cells and URAT1-expressing HEK293 cells. Amenamevir inhibited intracellular uptake of uric acid, a substrate of URAT1, by 38% at the highest concentration (100 μmol/L) investigated. Amenamevir, on the other hand, did not inhibit intracellular uptake of glycylsarcosine, a substrate of PEPT1 and PEPT2, within a concentration range investigated. Based on the above, the inhibitory effect of amenamevir against URAT1 was suggested, but no inhibitory effect was presented against PEPT1 or PEPT2.

4.R Outline of the review conducted by PMDA

PMDA has concluded that the submitted non-clinical PK study data of amenamevir raise no particular concerns.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted toxicity studies of amenamevir including single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (phototoxicity study, impurity toxicity study).

Unless otherwise specified, 5% hydroxypropylmethylcellulose solution was used as vehicle.

5.1 Single-dose toxicity (CTD 4.2.3.1-1, 4.2.3.1-2)

Mice (n = 6/sex/group) orally received single dose of amenamevir 0 (vehicle) or 500 mg/kg, and dogs (n = 1/sex/group) orally received single dose of amenamevir 0 (vehicle), 375, or 750 mg/kg. No deaths occurred. Thus, the approximate lethal dose was determined to be >500 mg/kg in mice and >750 mg/kg in dogs.

5.2 Repeated-dose toxicity

In repeated oral dose studies of amenamevir in mice (4 weeks, 13 weeks, 26 weeks) and dogs (4 weeks, 13 weeks, 52 weeks), effects on the liver were observed in both mice and dogs (increased weight, hepatocellular hypertrophy, hepatic necrosis, etc.). The applicant explained that increased liver weight, hepatocellular hypertrophy, and serum alkaline phosphatase (ALP) increased were changes attributable to induction of drug metabolism enzymes in the liver (*J Toxicol Pathol.* 2002;15: 49-59).

The plasma exposure (AUC_{0-24}) following 4-week administration at the no observed adverse effect level (NOAEL) (500 mg/kg/day in mice, 10 mg/kg/day in dogs) was 111,321 ng·h/mL in mice and 58,923 ng·h/mL in dogs, which were 4.9-fold and 2.6-fold, respectively, that at a clinical dose (400 mg/day)[5)] (area under the plasma concentration versus time curve over the dosing interval [AUC_{tau}], 22,943 ng·h/mL).

5.2.1 Four-week oral dose toxicity study in mice (CTD 4.2.3.2-2)

Amenamevir 0 (vehicle), 15, 60, 250, or 500 mg/kg/day was orally administered to mice (n = 12 or 18/sex/group) for 4 weeks[6)] (including evaluation for reversibility with 4-week recovery period). In ≥250 mg/kg/day groups, increased liver weight was observed. The applicant explained that this finding was a toxicologically insignificant change, because there were no histopathologically abnormal findings, and change was reversible after recovery period. Based on the above, the NOAEL was determined to be 500 mg/kg/day.

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5) Comparison with the estimated plasma exposure at a steady state following multiple doses in patients with herpes zoster [see Section 6.2.2.1]

6) The highest dose was established based on the feasibility such as the maximum concentration that could be prepared.

5.2.2 Thirteen-week oral dose toxicity study in mice (CTD 4.2.3.2-3)

Amenamevir 0 (vehicle), 15, 60, or 250 mg/kg/day was orally administered to mice (n = 12 or 18/sex/group) for 13 weeks[6] (including evaluation for reversibility with 4-week recovery period). There were no abnormalities, and thus the NOAEL was determined to be 250 mg/kg/day.

5.2.3 Twenty-six-week oral dose toxicity study in mice (CTD 4.2.3.2-4)

Amenamevir 0 (vehicle), 15, 60, or 250 mg/kg/day was orally administered to mice (n = 17 or 28/sex/group) for 26 weeks (including evaluation for reversibility with 13-week recovery period). Findings included decreases in serum albumin ratio and albumin/globulin ratio as well as increased liver weight in the ≥60 mg/kg/day groups; and increases in serum urea nitrogen and serum β-globulin ratio in the 250 mg/kg/day group. The applicant explained that the findings in the amenamevir groups were toxicologically insignificant changes, because any of them was slight; there were no histopathologically abnormal findings; and they were reversible after recovery period. Based on the above, the NOAEL was determined to be 250 mg/kg/day.

5.2.4 Four-week oral dose toxicity study in dogs (CTD 4.2.3.2-6)

Amenamevir 0 (vehicle), 3, 10, 30, or 250 mg/kg/day was orally administered to dogs (n = 3 or 5/sex/group) for 4 weeks (including evaluation for reversibility with 4-week recovery period). Findings included soft stool, increased serum ALP, and increased liver weight in the ≥ 30 mg/kg/day groups; and stool containing white matters, increased serum alanine aminotransferase (ALT), increased serum aspartate aminotransferase (AST), centrilobular hepatocellular hypertrophy, and hepatic single cell necrosis in the 250 mg/kg/day group. Any of the findings was reversible after recovery period. Based on the above, the NOAEL was determined to be 10 mg/kg/day.

5.2.5 Thirteen-week oral dose toxicity study in dogs (CTD 4.2.3.2-7, 4.2.3.2-8)

Amenamevir 0 (vehicle), 3, 10, 30, or 250 mg/kg/day was orally administered to dogs (n = 3 or 6/sex/group) for 13 weeks (including evaluation for reversibility with 4-week recovery period). In the 250 mg/kg/day group, some animals were found dead or moribund (1 of 6 males, 1 of 6 females), or treatment discontinued due to the aggravated condition (1 of 6 females). Findings in animals found dead or moribund included decreased locomotor activity, yellowing of conjunctiva/oral mucosa, decreased body weight, abnormalities in clinical chemistry (increases in serum AST, ALP, bilirubin, etc.), yellowing of subcutaneous tissue and various organs, effects on the liver (increased liver weight, degeneration of hepatocytes, single cell necrosis, biliary embolization in bile canaliculi, etc.), effects on the kidney (increased kidney weight, vacuolation in proximal renal tubule epithelial cells, focal hemorrhage, etc.), extramedullary hematopoiesis in the spleen, and hemorrhagic changes in various organs. Findings in the animal which discontinued the treatment included decreased locomotor activity, yellowing of conjunctiva/oral mucosa, decreased body weight, and increases in serum AST, ALP, and total bilirubin, but they were reversible after recovery period. Findings in surviving animals in the 250 mg/kg/day group included white stool containing test-article-like foreign matters, increased serum ALP, increases in liver and adrenal gland weights, and centrilobular hepatocellular hypertrophy. These findings, however, were reversible after recovery period. Because centrilobular hepatocellular hypertrophy was also observed in 1 female in the 30 mg/kg/day group, the NOAEL was determined to be 30 mg/kg/day in males and 10 mg/kg/day in females.

5.2.6 Fifty-two-week oral dose toxicity study in dogs (CTD 4.2.3.2-9)

Amenamevir 0 (vehicle), 3, 10, 30, or 60 mg/kg/day was orally administered to dogs (n = 4/sex/group) for 52 weeks. Findings included increased platelet count, increased serum ALP, centrilobular hepatocellular hypertrophy, and pigmented foamy macrophages in the adrenal gland in the ≥10 mg/kg/day groups; increases in liver and pancreas weights, enlarged liver, and hypertrophy of thyroid follicular epithelial cells in the ≥30 mg/kg/day groups; and increased serum ALT in the 60 mg/kg/day group. Based on the above, the NOAEL was determined to be 3 mg/kg/day.

5.3 Genotoxicity (CTD 4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1)

The applicant conducted genotoxicity studies of amenamevir including *in vitro* studies of bacterial reverse mutation assay (Ames test) and human lymphocyte chromosome aberration assay as well as an

in vivo study of mouse micronucleus assay. All the assays produced negative results, and thus amenamevir was determined to have no genotoxicity.

5.4 Carcinogenicity

Oral dose carcinogenicity studies were conducted in mice and rats. In either mice or rats, the tumorigenesis frequency did not increase, and thus amenamevir was determined to have no carcinogenicity. For both mice and rats, the highest dose was established based on the feasibility such as the maximum concentration that could be prepared.

The plasma exposure ($AUC_{0\text{-}24}$) at the non-carcinogenic dose (250 mg/kg/day in mice, 250 mg/kg/day in rats) was 116,707 ng·h/mL in mice (mean in both males and females), and 71,321 ng·h/mL in male rats and 210,111 ng·h/mL in female rats, of which the value in mice was 5.1-fold the plasma exposure[5)] (AUC_{tau}, 22,943 ng·h/mL) at the clinical dose (400 mg/day), and the values in rats were 3.1 to 9.2-fold.

5.4.1 A 104-week oral dose carcinogenicity study in mice (CTD 4.2.3.4.1-1)

Amenamevir 0 (vehicle), 60, 125, or 250 mg/kg/day was orally administered to mice (n = 60/sex/group) for 93 weeks. Although amenamevir had been planned to be orally administered for 104 weeks, the survival rate in Week 93 reached 35% to 45% in all the groups including the vehicle group, and thus the administration was discontinued. Amenamevir did not have any effect on the survival rate or body weight gain, and neither non-neoplastic lesions nor tumorigenesis frequency increased.

5.4.2 Preliminary study for 13-week oral dose carcinogenicity study in rats (CTD 4.2.3.4.1-3)

Amenamevir 0 (vehicle), 60, 125, or 250 mg/kg/day was orally administered to rats (n = 10/sex/group) for 13 weeks. Findings included increases in liver and kidney weights in the ≥60 mg/kg/day groups, and crystals in urine in the ≥125 mg/kg/day groups. The applicant explained that the findings in the ≥60 mg/kg/day groups were toxicologically insignificant, because there were no abnormalities in clinical chemistry nor histopathological findings. Based on the above, the NOAEL was determined to be 250 mg/kg/day.

5.4.3 A 104-week oral dose carcinogenicity study in rats (CTD 4.2.3.4.1-4)

Amenamevir 0 (vehicle or water for injection), 60, 125, or 250 mg/kg/day was orally administered to rats (n = 10/sex/group) for 104 weeks. Amenamevir did not have any effect on the survival rate or body weight gain, and neither non-neoplastic lesions nor tumorigenesis frequency increased.

5.5 Reproductive and developmental toxicity

The applicant conducted a study of fertility and early embryonic development in mice, embryo-fetal development toxicity studies in mice and rabbits, and a study on pre- and postnatal development in mice, including maternal function. Findings in mice included premature birth and all offspring's death in maternal animals, and decreased survival rate on postnatal day 4 in offspring; and findings in rabbits included death, abortion, premature birth, and reduced body weight gain in maternal animals. There were no effects on embryos or fetuses in either mice or rabbits. $AUC_{0\text{-}24}$ and C_{max}, parameter values of plasma exposure, in maternal animals at the NOAEL (500 mg/kg/day in mice, 250 mg/kg/day in rabbits) for embryo-fetal development were 121,620 ng·h/mL and 17,771 ng/mL, respectively, in mice and 213,758 ng·h/mL and 25,379 ng/mL, respectively, in rabbits, of which the values in mice were 5.3 and 9.1-fold the plasma exposure[5)] (AUC_{tau}, 22,943 ng·h/mL; C_{max}, 1943 ng/mL) at the clinical dose (400 mg/day), respectively; the values in rabbits were 9.3 and 13.1-fold, respectively.

5.5.1 Study of fertility and early embryonic development in mice (CTD 4.2.3.5.1-1 to 4.2.3.5.1-3)

Amenamevir 0 (vehicle), 15, 60, 250, or 500 mg/kg/day was orally administered to male mice from 2 weeks before mating through mating period to one day before necropsy and to female mice from 2 weeks before mating through mating period to Gestation Day 5 (n = 20/sex/group). In parent male and female animals, no abnormalities were observed in terms of the clinical sign, reproductive function, and early embryonic development. Based on the above, the NOAEL for clinical sign, reproductive function, and early embryonic development was determined to be 500 mg/kg/day.

5.5.2 Embryo-fetal development toxicity study in mice (CTD 4.2.3.5.2-2)

Amenamevir 0 (vehicle), 15, 60, 250, or 500 mg/kg/day was orally administered to pregnant mice (n = 20 or 21/group) from Gestation Day 5 to Gestation Day 17. In maternal animals, no abnormalities were observed in terms of clinical sign and embryo-fetal development. Based on the above, the NOAEL for maternal animals and embryo-fetal development was determined to be 500 mg/kg/day.

5.5.3 Embryo-fetal development toxicity study in rabbits (CTD 4.2.3.5.2-5)

Amenamevir 0 (vehicle), 30, 100, or 250 mg/kg/day was orally administered f to pregnant rabbits (n = 15-19/group) rom Gestation Day 6 to Gestation Day 18. In maternal animals in the 250 mg/kg/day group, death, abortion, and premature birth occurred. In animals that died, no changes were observed in clinical sign, body weight, or food consumption, and the necropsy did not present findings suggestive of a relationship to amenamevir. The applicant, therefore, explained that the death was not attributable to amenamevir. Findings in the 250 mg/kg/day group include reduced body weight gain and decreased food consumption in maternal animals; and increased ossification parameter in sacral and tail vertebrae in embryos and fetuses. The applicant explained that the increased ossification parameter was an incidental change, because it fell within a historical range at the testing facility. Based on the above, the NOAEL was determined to be 100 mg/kg/day for maternal animals and 250 mg/kg/day for embryos and fetuses.

5.5.4 Study on pre- and postnatal development in mice, including maternal function (CTD 4.2.3.5.3-1)

Amenamevir 0 (vehicle), 60, 250, or 500 mg/kg/day was orally administered to pregnant mice (n = 15-20/group) from Gestation Day 6 to Lactation Day 20 or 22. In maternal animals in the 500 mg/kg/day group, premature birth (1 of 16 females) and all offspring's death[7)] (2 of 16 females) occurred. In offspring in the 500 mg/kg/day group, reduced survival rate was observed on Postnatal Day 4. The applicant explained that the premature birth and all offspring's death observed in maternal animals were incidental changes, because such events were also included in the historical data at the testing facility. The applicant explained that the reduced survival rate on Postnatal Day 4 was a change associated with all offspring's death, but not attributable to amenamevir. Based on the above, the NOAEL for maternal animals and offspring was determined to be 500 mg/kg/day.

5.6 Other toxicity studies

5.6.1 Toxicity study of impurities (CTD 4.2.3.7.6-1 to 4.2.3.7.6-3)

For a degradation product (Substance A), of which concentration in the product possibly exceeds the qualification threshold defined in the "Revision of the Guideline for Impurities in New Drug Products" (PFSB/ELD Notification No. 0624001 dated June 24, 2003), the applicant conducted Ames test,[8)] *in silico* quantitative structure-activity relationship (QSAR) analysis in terms of the mutagenicity,[9)] human lymphocyte chromosome aberration assay,[8)] and 4-week repeated-dose toxicity study in dogs. Based on negative results from the Ames test and human lymphocyte chromosome aberration assay as well as results from the *in silico* QSAR analysis, Substance A was determined to have no genotoxicity. In the 4-week oral dose study in dogs (n = 3/sex/group), amenamevir containing Substance A at 2.51% was orally administered at 0 (vehicle), 5, or 10 mg/kg/day for 4 weeks, but no abnormalities were observed. The NOAEL of amenamevir containing Substance A at 2.51% was therefore determined to be 10 mg/kg/day. From the acceptance limit for Substance A ([redacted]%) and the clinical dose of amenamevir (400 mg/day), the maximum possible intake of impurities in humans was estimated to be [redacted] µg/kg/day. The applicant explained that the safety margin has approximately [redacted]-fold the dose in humans equivalent to the NOAEL (251 µg/kg/day) for the degradation products in the concerned study.

5.6.2 Phototoxicity study (CTD 4.2.3.7.7-1)

BALB/3T3 cells were added to amenamevir 0 (dimethyl sulfoxide), 7.8 to 1000 µg/mL or positive control substance (chlorpromazine, 0.016-40 µg/mL) under photoirradiation or without photoirradiation to investigate phototoxicity. Irrespective of with or without photoirradiation, no cytotoxicity was

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7) All of the offspring delivered through premature birth died until Lactation Day 2; and all of the offspring delivered by the other maternal animal died due to cannibalism until Lactation Day 5.

8) Amenamevir containing Substance A at 1.23% was used.

9) Analysis was performed using Derek Nexus 5.0.2.

observed in the cells with amenamevir at concentrations up to 130 μg/mL,[10] at which no deposition occurred.[11] Based on the above, amenamevir was determined to have no phototoxicity.

5.6.3 Investigation for hepatotoxicity (CTD 4.2.3.7.7-6)

Amenamevir 0 (vehicle), 3, 10, 60, or 250 mg/kg/day was orally administered to dogs for 4 weeks. Findings included hepatic CYP activity (increases in protein content in the liver, CYP content, testosterone 6β-hydroxylase activity) in the ≥3 mg/kg/day groups; enlarged liver, increased liver weight, and increased serum ALP in the ≥60 mg/kg/day groups; and increases in serum ALT and glutamate dehydrogenase, and centrilobular hepatocellular hypertrophy as well as hyperplasia of smooth endoplasmic reticulum in hepatocytes under electron microscopy in the 250 mg/kg/day group.

5.R Outline of the review conducted by PMDA

Toxicity evaluation of metabolites

PMDA asked the applicant to explain whether toxicity evaluation of metabolites was sufficient.

The applicant's explanation:

Following a single oral dose of ^{14}C-amenamevir 200 mg in healthy subjects, unchanged amenamevir and its metabolite, R5, were found in plasma [see Section 6.2.1.5]. In addition, in studies in which plasma PK of the metabolite, R5, was investigated following administration of amenamevir 400 mg, the exposure to the metabolite, R5, accounted for >10% of the total exposure[12] [see Sections 6.2.1.2 and 6.2.3.1]. The "'Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals' Questions and Answers (Q & A)" (Administrative Notice, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated August 16, 2012) has a description that toxicity of the metabolite is adequately characterized in general as long as its exposure in animals is ≥50% that in humans. Then, the plasma exposure ($AUC_{0\text{-}24}$) of the metabolite, R5, in the 60 mg/kg/day group in which no hepatotoxicity was observed in the investigation for hepatotoxicity in dogs following 4-week repeated oral administration [see Section 5.6.3] was compared with the plasma exposure[13] (area under the plasma concentration versus time curve extrapolated to infinite time [AUC_{inf}]) in subjects with severe renal impairment, which was found the highest [see Section 6.2.3.1]. As a result, the exposure to R5 in dogs was 5197 ng·h/mL, while that in humans was 5490 ng·h/mL. In addition, the plasma exposure to R5 was not determined in the 104-week oral dose carcinogenicity study in mice or embryo-fetal development toxicity study in mice, but the estimated plasma exposure[14] ($AUC_{0\text{-}24}$, 40,797 ng·h/mL; C_{max}, 10,655 ng/mL) to R5 at the non-carcinogenic dose (250 mg/kg/day) or NOAEL (500 mg/kg/day) in these studies [see Sections 5.4.1 and 5.5.2] were considered to exceed the plasma exposure (AUC_{inf}, 5490 ng·h/mL; C_{max}, 240 ng/mL) [see Section 6.2.3.1] to R5 in subjects with severe renal impairment. Based on the above, the applicant determined that toxicity evaluation of R5 was sufficient.

PMDA accepted the applicant's explanation.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

In clinical development, capsules containing 5, 25, 50, and 200 mg of amenamevir[15] as well as tablets containing 100 and 200 mg[16] were used as formulation containing amenamevir, and the 200 mg tablets were determined as the proposed commercial formulation (Amenalief).

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10) At the amenamevir concentration of 1000 μg/mL, deposition was observed.

11) Of the positive control substance, IC_{50} under photoirradiation/IC_{50} without photoirradiation was 42.2.

12) The sum of plasma exposure (AUC) to amenamevir and its metabolite, R5, was calculated to be the total exposure.

13) The applicant explained that the plasma exposure ($AUC_{0\text{-}24h}$) to R5 at the steady state following repeated administration of amenamevir is similar to that (AUC_{inf}) following a single dose.

14) Plasma exposure to R5 in female mice in the 250 mg/kg/day group on Day 28 in the 4-week repeated oral dose study in mice (CTD 4.2.2.2-3)

15) Used in phase I studies (Studies 15L-CL-001, 15L-CL-002, 15L-CL-003, 15L-CL-004, and 15L-CL-006).

16) Used in phase I studies (Studies 15L-CL-006, 15L-CL-008, 15L-CL-009, 15L-CL-010, 15L-CL-013, 15L-CL-014, 15L-CL-018, 15L-CL-019, M522101-EU21, M522101-EU22, M522101-EU23, M522101-EU24, M522101-EU25, M522101-J21, and M522101-J22), phase II studies (Studies 15L-CL-221 and 15L-CL-101), and phase III studies (Studies M522101-J01, M522101-J11, and M522101-J12).

In this section, data from biopharmaceutic study (relative bioavailability [BA] and food effect study) using the 200 mg capsules and 200 mg tablets are described. Concentrations of amenamevir and its major metabolite, R5, in human plasma and urine were measured by LC/MS/MS (lower limits of quantitation;, 1 or 5 ng/mL for amenamevir and 2 ng/mL for R5, respectively, in plasma, 1 or 50 ng/mL for amenamevir and 20 ng/mL for R5, respectively, in urine).

Doses and concentrations described hereinafter indicate the amount of amenamevir. Unless otherwise specified, PK parameters are expressed as the mean.

6.1.1 Investigation for relative BA and food effect (CTD 5.3.1.2-1, Study 15L-CL-006, [redacted] to [redacted])

A three-treatment, three-period crossover study[17] was conducted in non-Japanese healthy subjects (24 subjects included in PK analysis) to investigate the PK following a single oral dose of amenamevir capsules 800 mg under fasted conditions, or amenamevir tablets (Amenalief) 800 mg under fasted conditions or under fed conditions (high-fat diet with approximately 800-1000 kcal, containing fat at ≥50%). Results are as shown in Table 11.

Table 11. PK parameters of amenamevir following the amenamevir capsules or amenamevir tablets under fasted or fed conditions

	No. of subjects	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	t_{max}[a] (h)	$t_{1/2}$ (h)
Capsule (under fasted conditions)	24	2.27 (32.6)	28.1 (31.4)	2.0 [1.5, 4.0]	7.2 [5.7, 10.3]
Tablet (under fasted conditions)	24	2.01 (44.7)	24.1 (49.6)	2.0 [1.0, 8.0]	7.5 [5.9, 9.4]
Tablet (under fed conditions)	22	3.18 (19.2)	46.6 (28.3)	4.0 [3.0, 8.0]	7.1 [5.6, 9.5]

Geometric mean (Coefficient of variation [CV]%)
a) Median [range]

6.2 Clinical pharmacology

In this application, the applicant submitted clinical pharmacology data from studies in healthy subjects, in subjects with renal impairment, and in subjects with hepatic impairment and drug-drug interaction studies as well as population pharmacokinetics (PPK) analysis. Data from *in vitro* studies using human biological samples are described in non-clinical pharmacokinetics [see Sections 4.2 to 4.5].

6.2.1 Investigations in healthy subjects

6.2.1.1 Phase I study (CTD 5.3.3.1-1, Study 15L-CL-001, [redacted] to [redacted])

PK of amenamevir was investigated following a single oral dose of amenamevir capsules 5, 25, 100, 300, or 600 mg in Japanese healthy subjects (30 subjects included in PK analysis) under fasted conditions. The results are as shown in Table 12.

Table 12. PK parameters of amenamevir following a single dose of amenamevir capsules

Dose (mg)	No. of subjects	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	t_{max}[a] (h)	$t_{1/2}$[a] (h)	CL/F[b] (L/h)
5	6	0.04 (9.31)	0.46 (23.9)	1.8 [1.0, 3.0]	7.1 [6.5, 10.8]	11.1 ± 2.88
25	6	0.18 (12.40)	1.96 (15.3)	2.5 [1.0, 4.0]	7.5 [6.6, 8.1]	12.9 ± 2.04
100	6	0.52 (14.63)	5.66 (28.4)	2.0 [1.0, 3.0]	6.8 [5.2, 8.8]	18.4 ± 5.71
300	6	1.01 (25.36)	11.6 (16.4)	3.0 [2.0, 4.0]	6.9 [6.2, 7.6]	26.2 ± 4.49
600	6	1.66 (12.97)	18.5 (15.8)	3.0 [2.0, 4.0]	6.8 [6.2, 8.0]	32.7 ± 4.78

Geometric mean (CV%)
a) Median [range], b) Mean ± SD

6.2.1.2 Phase I study (Reference CTD 5.3.3.1-2, Study M522101-J21, [redacted] to [redacted])

PK of amenamevir and R5 was investigated following a single oral dose of amenamevir tablets 1200 mg or 2400 mg in Japanese healthy subjects (12 subjects included in PK analysis). The results are as shown in Table 13.

[17] Dosing periods were separated by a washout period for at least 6 days.

Table 13. PK parameters of amenamevir and R5 following a single dose of amenamevir

	Dose (mg)	No. of subjects	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	t_{max}[a] (h)	$t_{1/2}$[a] (h)	Cumulative excretion rate into urine (%)[b]
Amenamevir	1200	6	3.44 (28.1)	46.7 (30.4)	4.0 [3.0, 4.0]	7.1 [6.6, 7.4]	4.6
	2400	6	5.13 (26.4)	61.8 (20.5)	4.0 [1.0, 4.0]	6.6 [5.7, 7.2]	5.8
R5	1200	6	0.53 (24.5)	8.63 (26.8)	3.5 [3.0, 4.0]	8.0 [6.3, 8.3]	4.8
	2400	6	0.73 (51.3)	11.4 (42.5)	4.0 [3.0, 4.0]	7.1 [6.3, 8.2]	6.5

Geometric mean (CV%)
a) Median [range], b) Mean

6.2.1.3 Phase I study (CTD 5.3.3.3-1, Study 15L-CL-003, July 2006 to October 2006)

PK of amenamevir was investigated following 7-day oral administration of amenamevir capsules 300 or 600 mg quaque die (QD) to Japanese healthy subjects (subjects included in PK analysis; 12 non-elderly subjects aged ≥25 and <45 years, 12 elderly subjects aged ≥65 and <80 years) under fed conditions. PK parameters on Days 1 and 7 of treatment are as shown in Table 14. C_{max} and AUC_{inf} on Day 1 increased less than dose-proportionally in both non-elderly and elderly subjects. In addition, C_{max} and AUC_{inf} on Day 7 were similar to or lower than those on Day 1.

Table 14. PK parameters of amenamevir following multiple doses of amenamevir capsules

	Dose (mg)	No. of subjects	Date of measurement	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	t_{max}[a] (h)	$t_{1/2}$[a] (h)
Non-elderly	300	6	1	1.22 (28.5)	15.5 (27.8)	4.0 [1.5, 6.0]	7.6 [6.7, 8.7]
			7	1.29 (28.4)	15.2 (27.6)	4.0 [2.0, 4.0]	6.8 [5.8, 7.4]
	600	6	1	1.94 (23.1)	25.0 (32.9)	4.0 [4.0, 6.0]	7.8 [6.6, 8.4]
			7	1.90 (19.0)	21.8 (26.9)	4.0 [3.0, 4.0]	6.5 [5.9, 6.7]
Elderly	300	6	1	1.28 (19.3)	17.8 (21.7)	4.0 [4.0, 6.0]	9.3 [7.3, 11.3]
			7	1.15 (30.6)	15.3 (25.7)	4.0 [4.0, 6.0]	7.4 [6.3, 9.5]
	600	6	1	2.29 (22.8)	33.2 (31.4)	4.0 [3.0, 8.0]	8.5 [5.9, 12.1]
			7	2.09 (19.8)	25.7 (21.4)	3.5 [1.0, 4.0]	6.9 [5.5, 8.5]

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

6.2.1.4 Phase I study (Reference CTD 5.3.3.3-2, Study 15L-CL-004, [redacted] to [redacted])

PK of amenamevir was investigated following oral administration of amenamevir capsules 200, 400, 800, or 1200 mg QD in non-Japanese healthy subjects (32 subjects included in PK analysis) under fed conditions on Day 1 and Days 3 to 16. The results are as shown in Table 15.

Table 15. PK parameters of amenamevir following multiple doses of amenamevir capsules

Dose (mg)	No. of subjects	Date of measurement	C_{max} (μg/mL)	AUC[a] (μg·h/mL)	t_{max}[b] (h)	$t_{1/2}$[b] (h)
200	8	1	0.93 ± 0.27	12.6 ± 2.75	4.0 [2.0, 6.0]	7.4 [6.6, 9.5]
		16	1.00 ± 0.18	11.1 ± 1.96	4.0 [1.5, 6.0]	7.5 [6.1, 9.2]
400	8	1	2.06 ± 0.57 [b]	25.9 ± 7.95	3.0 [1.5, 4.0] [c]	7.9 [5.8, 10.4]
		16	1.88 ± 0.57	19.1 ± 6.02	3.5 [1.0, 4.0]	7.0 [5.9, 8.3]
800	8	1	2.82 ± 0.56	38.4 ± 7.58	3.5 [1.5, 4.0]	6.7 [5.8, 9.9]
		16	2.50 ± 0.77	25.8 ± 7.51	3.0 [1.0, 4.0]	6.2 [5.6, 8.5]
1200	8	1	4.45 ± 1.08	50.1 ± 14.2	2.0 [1.0, 4.0]	6.4 [4.8, 6.9]
		16	3.14 ± 0.99	28.3 ± 7.61	2.5 [0.5, 4.0]	6.1 [4.7, 7.4]

Mean ± SD
a) AUC_{inf} on Day 1, AUC_{tau} on Day 16, b) Median [range], c) n = 7

6.2.1.5 Mass balance study (Reference CTD 5.3.3.1-3, Study 15L-CL-007, [redacted] to [redacted])

Mass balance was investigated following a single oral dose of ^{14}C-amenamevir 200 mg in non-Japanese healthy subjects (6 subjects included in PK analysis). The excretion rates of radioactivity into urine and feces up to 168 hours post-dose were 20.6% and 74.6%, respectively.

6.2.2 Investigations in patients

6.2.2.1 PPK analysis (Reference CTD 5.3.5.1-1, Study 15L-CL-221, November 2007 to September 2008)

Using data on plasma amenamevir concentration at 621 measurement points in 223 patients with herpes zoster obtained from a phase II study (Study 15L-CL-221) [see Section 7.1], PPK analysis was

performed using software of NONMEM ver. 6. The final model was described as a 1-compartment model with first-order absorption in which the BA decreased with the increasing dose. The age was identified as a covariate on clearance.[18)] Table 16 shows PK parameters of amenamevir at a steady state in patients receiving amenamevir estimated using the final model.

In addition, PK parameters (C_{max}, AUC_{tau}, Time above 50, Time above 100, Time above 200, and Time above 400) estimated from the PPK analysis were investigated for relationships with PD parameters (cessation of new lesion formation, 50% crusting, complete crusting, healing, and days to virus disappearance), but none of the PK parameters were found related to any of the PD parameters.

Table 16. PK parameters of amenamevir at a steady state estimated using the final model

Dose (mg)	C_{max} (μg/mL)	AUC_{tau} (μg·h/mL)
100	0.76 ± 0.17	8.74 ± 1.94
200	1.26 ± 0.25	14.6 ± 3.25
400	1.94 ± 0.43	22.9 ± 4.92

Mean ± SD

6.2.3 Investigations of intrinsic factors

6.2.3.1 Study in subjects with renal impairment (Reference CTD 5.3.3.3-4, Study 15L-CL-014 [redacted] to [redacted])

PK of amenamevir and R5 was investigated following a single oral dose of amenamevir 400 mg in non-Japanese subjects with renal impairment[19)] (8 subjects for each of mild, moderate, and severe impairment) and non-Japanese subjects with normal renal function (9 subjects). The results are as shown in Table 17. AUC_{inf} tended to increase with the increasing severity of renal impairment [for the safety in patients with renal impairment, see Section 7.R.2.2].

Table 17. PK parameters of amenamevir and R5 in subjects with normal renal function and subjects with renal impairment

Severity of renal impairment	No. of subjects	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	C_{max} (non-bound) (μg/mL)	AUC_{inf} (non-bound) (μg·h/mL)
Amenamevir					
Normal	9	1.52 (33.3)	16.1 (33.1)	0.33 (35.8)	3.49 (33.4)
Mild	8	1.40 (31.2)	19.3 (24.7)	0.30 (31.5)	4.15 (23.0)
Moderate	8	1.50 (27.6)	21.7 (44.3)	0.33 (24.4)	4.80 (39.9)
Severe	8	1.78 (36.2)	28.6 (40.8)	0.41 (33.2)	6.52 (35.5)
R5					
Normal	9	0.17 (49.8)	2.15 (36.0)	-	-
Mild	8	0.19 (30.7)	3.16 (27.9)	-	-
Moderate	8	0.21 (23.1)	4.01 (23.1)	-	-
Severe	8	0.24 (36.3)	5.49 (41.6)	-	-

Geometric mean (CV%)
-, Not measured

6.2.3.2 Study in subjects with hepatic impairment (Reference CTD 5.3.3.3-3, Study 15L-CL-013, [redacted] to [redacted])

PK of amenamevir and R5 was investigated following a single oral dose of amenamevir 400 mg in 8 non-Japanese subjects with moderate hepatic impairment (Child-Pugh Class B) and 8 non-Japanese subjects with normal hepatic function. The results are as shown in Table 18.

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18) Age, sex, height, body weight, white blood cell count, red blood cell count, hemoglobin value, hematocrit value, platelet count, creatinine value, blood urea nitrogen value, albumin value, bilirubin value, AST value, ALT value, ALP value, total protein, and cholesterol value were considered as potential covariates.

19) Severity of renal impairment was rated based on CL_{cr} estimated according to Cockcroft-Gault equation (normal renal function, CL_{cr} >80 mL/min; mild renal impairment, CL_{cr} ≥50 mL/min and ≤80 mL/min; moderate, CL_{cr} ≥30 mL/min and <50 mL/min; severe, CL_{cr} <30 mL/min).

Table 18. PK parameters of amenamevir and R5 in subjects with normal hepatic function and subjects with hepatic impairment

Severity of hepatic impairment	No. of subjects	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	C_{max} (non-bound) (μg/mL)	AUC_{inf} (non-bound) (μg·h/mL)
Amenamevir					
Normal	8	1.33 (42.3)	15.2 (36.3)	0.29 (39.5)	3.35 (35.3)
Moderate	8	1.21 (44.8)	14.5 (26.7)	0.28 (47.3)	3.32 (27.2)
R5					
Normal	8	0.14 (53.3)	1.86 (38.9)	-	-
Moderate	8	0.10 (64.6)	1.39 (50.7)	-	-

Geometric mean (CV%)
-, Not measured

6.2.4 Investigation of pharmacokinetic interactions[20)]

A study to investigate drug-drug interaction of amenamevir with concomitant drugs was conducted. Table 19 and Table 20 show the least squares geometric mean ratio [90% confidence interval (CI)] of a PK parameter of amenamevir or a concomitant drug administered concomitantly relative to that of amenamevir or a concomitant drug administered alone. Based on these results, the applicant explained that cautions for concomitant use of CYP3A inducers and inhibitors, CYP3A and CYP2B6 substrates, and cyclosporine should be provided.

Table 19. Effects of concomitant drugs on PK parameters of amenamevir

Drug	Dosage and administration		No. of subjects	Least squares geometric mean ratio [90% CI]	
	Concomitant drug	Amenamevir		C_{max}	AUC_{inf}
Ketoconazole	400 mg QD	400 mg single dose	22	1.30 [1.17, 1.45]	2.58 [2.32, 2.87]
Rifampicin	600 mg QD	400 mg single dose	22	0.42 [0.37, 0.49]	0.17 [0.15, 0.19]
Cyclosporine	100 mg BID	400 or 1200 mg single dose	24	0.67 [0.63, 0.72]	0.80 [0.75, 0.86]
Ritonavir	600 mg single dose	400 mg single dose	24	1.36 [1.24, 1.51]	2.60 [2.34, 2.89]

Table 20. Effects of amenamevir on PK parameters of concomitant drugs

Drug	Dosage and administration		No. of subjects	Least squares geometric mean ratio [90% CI]	
	Concomitant drug	Amenamevir		C_{max}	AUC_{inf}
Montelukast	10 mg single dose	400 mg single dose	24	1.22 [1.15, 1.29]	1.22 [1.16, 1.28]
Midazolam	7.5 mg single dose	400 mg QD	18	0.68 [0.59, 0.78]	0.51 [0.47, 0.56]
Bupropion	150 mg single dose	400 mg QD	24	0.84 [0.78, 0.91]	0.84 [0.79, 0.90]
Warfarin	25 mg single dose	400 mg QD	15[a)]	1.08 [1.02, 1.15]	0.92 [0.89, 0.96]

a) 17 subjects received the drug alone.

6.2.5 QT/QTc study (Reference CTD 5.3.4.1-1, Study M522101-J22, [redacted] to [redacted])[21)]

A five-treatment, five-period crossover study was conducted in 46 Japanese healthy subjects to investigate effects of amenamevir on QT/corrected QT (QTc) interval. In this study, a single oral dose of placebo, or amenamevir 400, 1200, or 2400 mg was administered, while a single oral dose of moxifloxacin 400 mg was used as the positive control. Differences in estimated change in Fridericia-corrected QT (QTcF) interval from baseline between the amenamevir and placebo groups were −2.63 msec to 2.12 msec. Because the upper limit of 95% confidence interval was below 10 msec at any measurement timepoint, the applicant explained that amenamevir would not affect QTcF within the dose range from 400 to 2400 mg. In addition, C_{max} and area under the plasma concentration versus time curve (AUC) following administration of amenamevir were 1.48 μg/mL and 19.9 μg·h/mL, respectively, in the 400 mg group; 3.09 μg/mL and 43.3 μg·h/mL, respectively, in the 1200 mg group; and 4.63 μg/mL and 63.0 μg·h/mL, respectively, in the 2400 mg group.

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20) Reference CTD 5.3.3.4-1, Study 15L-CL-008 ([redacted] to [redacted]); Reference CTD 5.3.3.4-2, Study 15L-CL-009 ([redacted] to [redacted]); Reference CTD 5.3.3.4-3, Study 15L-CL-010 ([redacted] to [redacted]); Reference CTD 5.3.3.4-4, Study 15L-CL-018 ([redacted] to [redacted]); Reference CTD 5.3.3.4-5, Study M522101-EU21 (October 2014 to February 2015); Reference CTD 5.3.3.4-6, Study M522101-EU22 (September 2014 to December 2014); Reference CTD 5.3.3.4-7, Study M522101-EU23 (December 2014 to April 2015); Reference CTD 5.3.3.4-8, Study M522101-EU24 (March 2015 to May 2015); Reference CTD 5.3.3.4-9, Study M522101-EU25 (February 2015 to April 2015)

21) Because [redacted] was found at the site of this study, consultation about [redacted] was held [redacted], and data from this study were decided to be handled as reference data in this application.

6.R Outline of the review conducted by PMDA

6.R.1 Food effect on PK of amenamevir

The applicant's explanation on provisions for a diet in the proposed administration:

Results from investigation of the food effect on PK of amenamevir showed that C_{max} and AUC_{inf} of amenamevir following administration under fed conditions (high-fat diet) were 1.55 and 1.92-fold higher than the corresponding parameter values following administration under fasted conditions [see Section 6.1.1]. In phase II and phase III studies, therefore, amenamevir was to be administered under fed conditions to evaluate the efficacy and safety [see Sections 7.1 and 7.2]. The phase III study demonstrated the efficacy and safety of amenamevir, and amenamevir was proposed to be administered under fed conditions.

PMDA has concluded that administration of amenamevir only under fed conditions is acceptable, based on data on the efficacy and safety from the phase III study in which amenamevir was administered under fed conditions, although the food effect on PK of amenamevir was investigated only with a high-fat diet, and thus the effect of pre-dose food other than the high-fat diet remains unknown. In addition, the efficacy and safety of amenamevir are discussed in Section 7.R.

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

The applicant submitted data on the efficacy and safety of amenamevir from each of phase II and phase III studies in patients with herpes zoster (Studies 15L-CL-221 and M522101-J01) in this application. The summary of the major clinical studies is as shown in Table 21.

Table 21. Summary of major clinical studies

Phase	Study No.	Study population	Major purpose	Dosage regimen	No. of subjects
II	Study 15L-CL-221 (reference data)	Patients with herpes zoster	Efficacy Safety	(a) Amenamevir 100 mg group, amenamevir 100 mg QD for 7 days (b) Amenamevir 200 mg group, amenamevir 200 mg QD for 7 days (c) Amenamevir 400 mg group, amenamevir 400 mg QD for 7 days (d) VACV group, VACV 1000 mg TID for 7 days	(a) 75 (b) 80 (c) 68 (d) 73
III	Study M522101-J01 (evaluation data)	Patients with herpes zoster	Efficacy Safety	(a) Amenamevir 200 mg group, amenamevir 200 mg QD for 7 days (b) Amenamevir 400 mg group, amenamevir 400 mg QD for 7 days (c) VACV group, VACV 1000 mg TID for 7 days	(a) 252 (b) 249 (c) 249

7.1 Phase II study (Reference CTD 5.3.5.1-1, Study 15L-CL-221, November 2007 to September 2008)

A randomized, double-blind, parallel-group study was conducted in patients with herpes zoster (target sample size, 400 subjects [100 per group]) within 72 hours after onset of rash to investigate the efficacy and safety of amenamevir using VACV as the control at 53 study sites in Japan.

In the amenamevir groups, amenamevir 100, 200, or 400 mg was to be orally administered QD for 7 days under fed conditions, and in the VACV group, VACV 1000 mg was to be orally administered ter in die (TID) for 7 days under fed conditions.

Of 403 subjects who were randomized and received the study drug (102 in the amenamevir 100 mg group, 102 in the amenamevir 200 mg group, 97 in the amenamevir 400 mg group, 102 in the VACV group), 107 subjects whose source documents were not retained [see Section 8] were excluded, and the remaining 296 subjects (75 in the amenamevir 100 mg group, 80 in the amenamevir 200 mg group, 68 in the amenamevir 400 mg group, 73 in the VACV group) were included in the safety analysis set. Of these, 10 subjects in whom herpes zoster was denied by virological test after the start of the study drug administration were further excluded, and the remaining 286 subjects (73 in the amenamevir 100 mg group, 76 in the amenamevir 200 mg group, 66 in the amenamevir 400 mg group, 71 in the VACV group) were included in the full analysis set (FAS) and also in the efficacy analysis set.

The efficacy primary endpoint was percentage of subjects who achieved cessation of new lesion formation by Day 4 of the study drug administration (percentage of cessation of new lesion formation), and the concerned percentage in each group was 87.7% (64 of 73) of subjects in the amenamevir 100

mg group, 85.5% (65 of 76) of subjects in the amenamevir 200 mg group, 90.9% (60 of 66) of subjects in the amenamevir 400 mg group, and 87.3% (62 of 71) of subjects in the VACV group.

The incidence of adverse events (including abnormal laboratory changes) was 60.0% (45 of 75) of subjects in the amenamevir 100 mg group, 55.0% (44 of 80) of subjects in the amenamevir 200 mg group, 57.4% (39 of 68) of subjects in the amenamevir 400 mg group, and 58.9% (43 of 73) of subjects in the VACV group, and the incidence of adverse drug reactions[22)] (including abnormal laboratory changes) was 29.3% (22 of 75) of subjects in the amenamevir 100 mg group, 25.0% (20 of 80) of subjects in the amenamevir 200 mg group, 30.9% (21 of 68) of subjects in the amenamevir 400 mg group, and 21.9% (16 of 73) of subjects in the VACV group. Adverse events and adverse drug reactions with an incidence of ≥3% in any group are as shown in Table 22.

Table 22. Adverse events and adverse drug reactions with an incidence of ≥3% in any group (safety analysis set)

Event	Adverse events				Adverse drug reactions			
	Amenamevir 100 mg (n = 75)	Amenamevir 200 mg (n = 80)	Amenamevir 400 mg (n = 68)	VACV (n = 73)	Amenamevir 100 mg (n = 75)	Amenamevir 200 mg (n = 80)	Amenamevir 400 mg (n = 68)	VACV (n = 73)
Overall	45 (60.0)	44 (55.0)	39 (57.4)	43 (58.9)	22 (29.3)	20 (25.0)	21 (30.9)	16 (21.9)
NAG increased	2 (2.7)	7 (8.8)	8 (11.8)	2 (2.7)	1 (1.3)	3 (3.8)	6 (8.8)	2 (2.7)
α1-MG urine increased	3 (4.0)	5 (6.3)	6 (8.8)	5 (6.8)	1 (1.3)	3 (3.8)	3 (4.4)	2 (2.7)
Dermatitis contact	0	2 (2.5)	5 (7.4)	2 (2.7)	0	0	0	0
Blood ALP increased	4 (5.3)	0	4 (5.9)	0	4 (5.3)	0	3 (4.4)	0
Blood uric acid increased	3 (4.0)	3 (3.8)	3 (4.4)	2 (2.7)	2 (2.7)	1 (1.3)	2 (2.9)	0
Back pain	1 (1.3)	0	3 (4.4)	0	0	0	0	0
Nasopharyngitis	6 (8.0)	6 (7.5)	2 (2.9)	5 (6.8)	0	1 (1.3)	0	0
Glucose urine present	1 (1.3)	2 (2.5)	2 (2.9)	4 (5.5)	1 (1.3)	1 (1.3)	1 (1.5)	2 (2.7)
Eczema asteatotic	3 (4.0)	0	2 (2.9)	1 (1.4)	0	0	0	0
Urticaria	3 (4.0)	0	2 (2.9)	1 (1.4)	0	0	0	0
Diarrhoea	3 (4.0)	1 (1.3)	1 (1.5)	3 (4.1)	1 (1.3)	0	0	0
Blood potassium increased	3 (4.0)	1 (1.3)	1 (1.5)	0	2 (2.7)	1 (1.3)	0	0
ALT increased	1 (1.3)	1 (1.3)	1 (1.5)	4 (5.5)	1 (1.3)	1 (1.3)	1 (1.5)	3 (4.1)
Constipation	3 (4.0)	0	1 (1.5)	0	1 (1.3)	0	0	0
Headache	1 (1.3)	1 (1.3)	0	3 (4.1)	0	0	0	1 (1.4)
Seasonal allergy	0	1 (1.3)	0	3 (4.1)	0	0	0	0

No. of subjects (%)

No deaths occurred. Serious adverse events were reported by 3 subjects in the amenamevir 100 mg group (uterine cancer, gastric cancer, and neutrophil count decreased in 1 subject each), 1 subject in the amenamevir 200 mg group (spinal osteoarthritis), and 1 subject in the amenamevir 400 mg group (appendicitis), but a causal relationship of any event was ruled out. In terms of the outcome, neutrophil count decreased and appendicitis resolved, but the other events were unknown.

Adverse events leading to discontinuation were reported by 1 subject in the amenamevir 100 mg group (neutrophil count decreased) and 1 subject in the amenamevir 400 mg group (dermatitis contact), and a causal relationship of any event was ruled out. In terms of the outcome, neutrophil count decreased was resolving, and dermatitis contact did not resolve.

7.2 Phase III Study (CTD 5.3.5.1-2, Study M522101-J01, September 2013 to July 2015)

A randomized, double-blind, parallel-group study was conducted in patients with herpes zoster (target sample size, 750 subjects [250 per group]) within 72 hours after onset of rash to investigate the efficacy and safety of amenamevir using VACV as the control at 106 study sites in Japan.

In the amenamevir 200 or 400 mg group, amenamevir 200 or 400 mg was to be orally administered QD for 7 days under fed conditions, and in the VACV group, VACV 1000 mg was to be orally administered TID for 7 days under fed conditions.

All of 750 subjects who were randomized and received the study drug (252 in the amenamevir 200 mg group, 249 in the amenamevir 400 mg group, 249 in the VACV group) were included in the safety analysis set. Of these, 14 subjects in whom herpes zoster was denied by virological test after the start of

22) Adverse events for which a causal relationship to the study drug could not be ruled out

the study drug administration and 1 subject with missing efficacy data were excluded, and the remaining 735 subjects (247 in the amenamevir 200 mg group, 243 in the amenamevir 400 mg group, 245 in the VACV group) were included in the FAS and also in the efficacy analysis set.

The percentage of cessation of new lesion formation by Day 4, the efficacy primary endpoint, in each group is as shown in Table 23. The lower limit of 95% confidence interval of the difference between the amenamevir 400 mg and VACV groups was above the pre-determined non-inferiority margin (−10%), verifying non-inferiority of amenamevir 400 mg to VACV. Non-inferiority of amenamevir 200 mg to VACV, however, was not verified, because the lower limit of 95% confidence interval of the difference between amenamevir 200 mg and VACV groups was not above the pre-determined non-inferiority margin (−10%).

Table 23. Percentage of cessation of new lesion formation by Day 4 (FAS)

	Amenamevir 200 mg (n = 247)	Amenamevir 400 mg (n = 243)	VACV (n = 245)
Percentage of cessation of new lesion formation (%)	69.6 (172/247)	81.1 (197/243)	75.1 (184/245)
Difference from VACV [95% CI][a)] (%)	-4.3 [-12.0, 3.4]	7.1 [-0.2, 14.4]	

a) Adjusted by Mantel-Haenszel method using time from onset of rash to the start of the study drug administration (≤24 hours; >24 hours and ≤48 hours; >48 hours and ≤72 hours) and age (<65 years, ≥65 years) for stratification.

b) Multiplicity of the test was adjusted according to the following statistical test plan: In Step 1, non-inferiority of amenamevir 400 mg to VACV was tested; and if non-inferiority was verified in Step 1, non-inferiority of amenamevir 200 mg to VACV was tested in Step 2.

The incidence of adverse events (including abnormal laboratory changes) was 45.6% (115 of 252) of subjects in the amenamevir 200 mg group, 46.6% (116 of 249) of subjects in the amenamevir 400 mg group, and 45.4% (113 of 249) of subjects in the VACV group, and the incidence of adverse drug reactions (including abnormal laboratory changes)[22)] was 10.7% (27 of 252) of subjects in the amenamevir 200 mg group, 10.0% (25 of 249) of subjects in the amenamevir 400 mg group, and 12.0% (30 of 249) of subjects in the VACV group. Adverse events and adverse drug reactions with an incidence of ≥2% in any group are as shown in Table 24.

Table 24. Adverse events and adverse drug reactions with an incidence of ≥2% in any group (safety analysis set)

	Adverse events			Adverse drug reactions		
	Amenamevir 200 mg (n = 252)	Amenamevir 400 mg (n = 249)	VACV (n = 249)	Amenamevir 200 mg (n = 252)	Amenamevir 400 mg (n = 249)	VACV (n = 249)
Overall	115 (45.6)	116 (46.6)	113 (45.4)	27 (10.7)	25 (10.0)	30 (12.0)
Nasopharyngitis	19 (7.5)	22 (8.8)	17 (6.8)	0	0	0
NAG increased	7 (2.8)	11 (4.4)	8 (3.2)	4 (1.6)	3 (1.2)	2 (0.8)
α1-MG urine increased	11 (4.4)	9 (3.6)	10 (4.0)	6 (2.4)	3 (1.2)	4 (1.6)
Fibrin degradation products increased	7 (2.8)	9 (3.6)	10 (4.0)	4 (1.6)	5 (2.0)	6 (2.4)
Stomatitis	1 (0.4)	7 (2.8)	0	0	0	0
Dermatitis contact	4 (1.6)	5 (2.0)	5 (2.0)	0	0	0
Protein urine present	2 (0.8)	5 (2.0)	5 (2.0)	1 (0.4)	0	3 (1.2)
Glucose urine present	3 (1.2)	3 (1.2)	5 (2.0)	2 (0.8)	1 (0.4)	0
Eczema	7 (2.8)	3 (1.2)	6 (2.4)	0	0	0
Headache	9 (3.6)	2 (0.8)	7 (2.8)	1 (0.4)	0	2 (0.8)
Diarrhoea	1 (0.4)	2 (0.8)	5 (2.0)	0	1 (0.4)	3 (1.2)
Folliculitis	5 (2.0)	0	5 (2.0)	0	0	0

No. of subjects (%)

No deaths occurred. Serious adverse events were reported by 1 subject in the amenamevir 200 mg group (angina pectoris), 1 subject in the amenamevir 400 mg group (infectious mononucleosis), and 3 subjects in the VACV group (loss of consciousness, embolic cerebral infarction, lung neoplasm malignant, and tendon rupture in 1 subject each [including duplicate counting]), but a causal relationship of any event to the study drug was ruled out. In terms of the outcome, embolic cerebral infarction resolved with sequelae; lung neoplasm malignant did not resolve; and the other events were resolving or resolved.

Adverse events leading to discontinuation were reported by 1 subject in the amenamevir 200 mg group (headache and nausea) and 2 subjects in the VACV group (abdominal pain, hepatic function abnormal, encephalopathy in 1 subject each [including duplicate counting]). A causal relationship to the study drug could not be ruled out for all events, but all of them resolved following discontinuation of the study drug.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

As a result of the review described below, PMDA has concluded that amenamevir 400 mg is expected to be effective in patients with herpes zoster.

However, there are no clinical studies in patients with herpes zoster who have received ACV, VACV, or famciclovir (FCV), and the efficacy of amenamevir in these patients remains unknown. The applicant, therefore, should collect information on the efficacy of amenamevir in patients with herpes zoster who have received ACV, VACV, or FCV (including information on response to the previous treatment) after the market launch, and provide the obtained information to healthcare professionals appropriately. In addition, because clinical experience of amenamevir in the elderly is limited, the applicant should collect information on the efficacy of amenamevir in the elderly after the market launch, and provide the obtained information to healthcare professionals appropriately.

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

7.R.1.1 Efficacy

The applicant's explanation on the efficacy of amenamevir in patients with herpes zoster:
Data on the efficacy primary and secondary endpoints in the phase III study (Study M522101-J01) are as shown in Table 25, and in terms of the percentage of cessation of new lesion formation by Day 4, the primary endpoint, non-inferiority of amenamevir 400 mg to VACV was verified. Non-inferiority of amenamevir 200 mg to VACV, on the other hand, was not verified [see Section 7.2]. In addition, results on days to cessation of new lesion formation, complete crusting, and healing, the secondary endpoints, in the amenamevir 400 mg group were similar to those in the VACV group.

Table 26 shows results on percentage of cessation of new lesion formation by Day 4 in the amenamevir 400 mg and VACV groups by age, number of rashes at baseline, or time from onset of rash to the first dose. The efficacy of amenamevir remained consistent irrespective of the number of rashes at baseline and time from onset of rash to the first dose. In subgroups divided by age, the percentage of cessation of new lesion formation by Day 4 in the elderly ≥65 years in the amenamevir 400 mg group was lower than that in the non-elderly <65 years. In general, when herpes zoster is not treated with antiviral drugs, period to healing tends to be longer in the elderly than in the non-elderly (*Journal of Pediatric Dermatology.* 1993;12:13-6), and also in Study M522101-J01, the number of days to complete crusting and healing, the secondary endpoints, tended to be longer in the elderly in both amenamevir 400 mg and VACV groups. This longer period to healing in the elderly is considered partially responsible for the lower percentage of cessation of new lesion formation by Day 4 in the elderly than in the non-elderly. In the elderly ≥65 years, however, the number of days to complete crusting and healing (median) was 9 and 13 days, respectively, in the amenamevir 400 mg group and 10 and 15 days, respectively, in the VACV group; distribution of the actual numbers of days in the amenamevir 400 mg group was similar to that in the VACV group. Therefore, amenamevir 400 mg is expected to be effective even in the elderly at a certain level as with VACV.

Based on the above, the applicant considered that amenamevir 400 mg is expected to be effective in patients with herpes zoster.

Table 25. Efficacy in phase III study (Study M522101-J01) (FAS)

	Amenamevir 400 mg (n = 243)	Amenamevir 200 mg (n = 247)	VACV (n = 245)
Percentage of cessation of new lesion formation by Day 4 (%)	81.1	69.6	75.1
Difference from VACV [95% CI][a] (%)	7.1 [-0.2, 14.4]	-4.3 [-12.0, 3.4]	
Number of days to cessation of new lesion formation (days)[b]	4	4	4
Hazard ratio [95% CI][c]	1.06 [0.88, 1.28]	0.92 [0.76, 1.11]	
Number of days to complete crusting (days)[b]	9	8	8
Hazard ratio [95% CI][c]	0.99 [0.82, 1.20]	1.08 [0.89, 1.30]	
Number of days to healing (days)[b]	11	11	11
Hazard ratio [95% CI][c]	1.02 [0.84, 1.23]	0.99 [0.82, 1.20]	

a) Adjusted by Mantel-Haenszel method using time from onset of rash to the first dose of the study drug (≤24 hours; >24 hours and ≤48 hours; >48 hours and ≤72 hours) and age (<65 years, ≥65 years) for stratification.
b) Median
c) Stratified Cox proportional Hazards model using time from onset of rash to the first dose of the study drug (≤24 hours; >24 hours and ≤48 hours; >48 hours and ≤72 hours) for stratification.

Table 26. Percentage of cessation of new lesion formation by Day 4 by subgroup

		Amenamevir 400 mg (n = 243)	VACV (n = 245)
Age	<65 years	86.2% (150/174)	75.8% (135/178)
	≥65 years	68.1% (47/69)	73.1% (49/67)
Number of rashes at baseline	≥1 and <50	81.1% (99/122)	71.1% (86/121)
	≥50 and <100	83.9% (52/62)	78.3% (47/60)
	≥100	78.0% (46/59)	79.7% (51/64)
Time from onset of rash to the first dose	≤24 hours	75.0% (42/56)	53.3% (24/45)
	≥24 hours and ≤48 hours	82.7% (81/98)	75.8% (69/91)
	≥48 hours and ≤72 hours	83.1% (74/89)	83.5% (91/109)

PMDA's view:
Data on percentage of cessation of new lesion formation by Day 4 in Study M522101-J01 have verified non-inferiority of amenamevir 400 mg to VACV, and furthermore results on number of days to cessation of new lesion formation, complete crusting, and healing in the amenamevir 400 mg group were confirmed to be similar to those in the VACV group. Therefore, amenamevir 400 mg is expected to be effective in patients with herpes zoster. Although the number of subjects was limited, the percentage of cessation of new lesion formation by Day 4 in patients aged ≥65 years was lower than that in patients aged <65 years. Furthermore, the elderly is supposed to account for a large proportion of patients with herpes zoster. The applicant, therefore, should collect information on the efficacy in elderly patients after the market launch, and provide the obtained information to healthcare professionals appropriately.

7.R.1.2 PHN after administration of amenamevir

The applicant's explanation on PHN after administration of amenamevir:
PHN is a neuropathic pain caused by nerve degeneration resulting from viral infection, and the pain may persist for several months even after disappearance of skin symptoms of herpes zoster. In treatment of herpes zoster, suppression against transition to PHN is important, and a suppressive effect of amenamevir against transition to PHN was investigated in a Japanese clinical study. Herpes zoster-associated pain is classified as prodromal pain, acute herpes zoster pain, or PHN. Both acute herpes zoster pain and PHN, however, exist for a certain period, and it is difficult to classify herpes zoster-associated pain clearly. In published literature (*Neurological Therapeutics.* 2010;27:593-622, *Journal of Clinical Therapeutics & Medicines.* 2012;28:161-73, *Int J Infect Dis.* 2015;34:126-31), PHN is defined as a pain persisting for ≥3 months,[23] and thus PHN was defined as "pain that remains 91 or 92 days after the start of the study drug administration" in clinical studies of amenamevir. The incidence of PHN in clinical studies of amenamevir was 3.0% (2 of 66) of subjects in the amenamevir 400 mg group, 0.0% (0 of 96) of subjects in the amenamevir 200 mg group, 2.7% (2 of 73) of subjects in the amenamevir 100 mg group, and 0.0% (0 of 71) of subjects in the VACV group in the phase II study

[23] In the Clinical Practice Guideline for Chronic Pain edited by the Japanese Society of Neurological Therapeutics, PHN is classified as chronic pain, which is defined as pain that persists for ≥ 3 months (*Neurological therapeutics.* 2010; 27: 593-622). The Expert Consensus on Herpes Zoster: Diagnosis, Treatment and Prevention instructs that the therapeutic effect for PHN should be assessed based on treatment data in patients in whom at least 3 months have passed since onset of herpes zoster (*Journal of Clinical Therapeutics & Medicines.* 2012;28:161-73). In a recent foreign cohort study, PHN is defined as a pain that exists at least 90 days after onset of herpes and is rated as the Numerical Rating Scale ≥3 (*Int J Infect Dis.* 2015;34:126-31).

(Study 15L-CL-221); and 1.0% (2 of 193) of subjects in the amenamevir 400 mg group, 1.9% (4 of 209) of subjects in the amenamevir 200 mg group, and 1.0% (2 of 206) of subjects in the VACV group in the phase III study (Study M522101-J01). In consideration that the incidence of PHN in patients with herpes zoster left untreated without antiviral drugs was reported to be approximately 10% (*J Int Med Res.* 2002;30:56-65, *Clin Infect Dis.* 1996;22:341-347), amenamevir 400 mg was expected to suppress transition to PHN as with VACV.

Based on results from Japanese clinical studies, PMDA confirmed that the effect against "pain that remains 91 or 92 days after the start of the study drug administration" in the amenamevir 400 mg group was similar to that in the VACV group, and thus has concluded that amenamevir is expected to have a suppressive effect against PHN as with VACV.

7.R.2 Safety

As a result of the review described below, PMDA has concluded that the safety of amenamevir 400 mg in patients with herpes zoster is acceptable.

The applicant, however, should collect information on the safety of amenamevir in patients with hepatic impairment, patients with renal impairment, and the elderly after the market launch continuously, and provide the obtained information to healthcare professionals appropriately.

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

7.R.2.1 Summary of the safety of amenamevir

The applicant's explanation on the safety of amenamevir:

Table 27 shows the summary of the submitted data on the safety of amenamevir in phase II and phase III studies in patients with herpes zoster (Studies 15L-CL-221 and M522101-J01) and phase III studies in patients with herpes simplex (Studies M522101-J11 and M522101-J12).[24)] Adverse events and adverse drug reactions in patients with herpes zoster receiving amenamevir were consistent irrespective of the dose of amenamevir, and were similar to those in patients receiving VACV. In addition, no particular differences were observed in contents of the events among the dose groups [see Sections 7.1 and 7.2].

Table 27. Summary of the safety in Japanese clinical studies in patients with herpes zoster or with herpes simplex (safety analysis set)

	Patients with herpes zoster (Studies 15L-CL-221 and M522101-J01)				Patients with herpes simplex (Studies M522101-J11 and M522101-J12)	
	Amenamevir 400 mg (n = 317)	Amenamevir 200 mg (n = 332)	Amenamevir 100 mg (n = 75)	VACV (n = 322)	Amenamevir 200 mg (n = 580)	Placebo (n = 157)
Adverse events	155 (48.9)	159 (47.9)	45 (60.0)	156 (48.4)	267 (46.0)	59 (37.6)
Adverse drug reactions	46 (14.5)	47 (14.2)	22 (29.3)	46 (14.3)	73 (12.6)	12 (7.6)
Deaths	0	0	0	0	0	0
Grade ≥3 adverse events[a)]	0	0	1 (1.3)	2 (0.6)	4 (0.7)	1 (0.6)
Serious adverse events	2 (0.6)	1 (0.3)	2 (2.7)	3 (0.9)	2 (0.3)	0
Adverse events leading to discontinuation	1 (0.3)	1 (0.3)	1 (1.3)	2 (0.6)	1 (0.2)	0

No. of subjects (%)

a) Adverse events assessed at Grade ≥3 in accordance with the "Criteria of Severity of Adverse Drug Reactions for Drugs, etc." (PAB/SD Notification No. 80 dated June 29, 1992)

In patients with herpes zoster receiving amenamevir, serious adverse events were reported by 2 subjects in the 400 mg group (appendicitis and infectious mononucleosis in 1 subject each), 2 subjects in the 200 mg group (spinal osteoarthritis and angina pectoris in 1 subject each), and 3 subjects in the 100 mg group (uterine cancer, gastric cancer, and neutrophil count decreased in 1 subject each). In patients with herpes simplex receiving amenamevir, serious adverse events were reported by 6 subjects (cellulitis of

[24)] Study M522101-J11, a placebo-controlled, double-blind, parallel-group study in patients with herpes simplex (labial or facial herpes or recurrent genital herpes) (CTD 5.3.5.4-2); Study M522101-J12, an open-label uncontrolled study in patients with herpes simplex (recurrent labial or facial herpes, recurrent genital herpes, or Kaposi's varicelliform eruption) (CTD 5.3.5.4-3). In any study, patients received amenamevir 200 mg QD in the morning for 5 days under fed conditions.

male external genital organ, progressive facial hemiatrophy, cervical dysplasia, breast cancer, foot fracture, and cataract in 1 subject each). A causal relationship to amenamevir was ruled out for all events.

In patients with herpes zoster receiving amenamevir, adverse events leading to discontinuation were reported by 1 subject in the 400 mg group (dermatitis contact), 1 subject in the 200 mg group (headache and nausea), and 1 subject in the 100 mg group (neutrophil count decreased). In patients with herpes simplex receiving amenamevir, adverse events leading to discontinuation were reported by 1 subject in the 200 mg group (back pain). A causal relationship to amenamevir could not be ruled out for headache and nausea, but both were non-serious and resolved after discontinuation.

PMDA's view:
In consideration of Grade ≥3 adverse events and serious adverse events in Japanese clinical studies as well as reviews in 7.R.2.1 to 5 below, the safety of amenamevir is acceptable. The applicant, however, should collect the post-marketing information on the safety of amenamevir in patients with hepatic impairment, and provide the obtained information to healthcare professionals appropriately, because PK of amenamevir in subjects with severe hepatic impairment has not been investigated in the clinical pharmacology study [see Section 6.2.3.2]; and effects on the liver were observed in repeated-dose toxicity studies [see Sections 5.2 and 5.6.3], although in clinical studies, no serious adverse events related to hepatic function were reported in subjects receiving amenamevir, and there are no particular concerns about effects on the liver at present.

In the following sections, the effect on renal function, platelet count decreased, and effect on the cardiovascular system in patients receiving amenamevir as well as the safety of amenamevir in the elderly are described in detail.

7.R.2.2 Effect on renal function

The applicant's explanation on the effect of amenamevir on renal function:
(a) Renal tubular disorder associated with amenamevir
In the foreign phase I study, a crystal-like substance considered to be the drug was observed in urine specimens collected from subjects.[25)] In the phase III study in patients with herpes zoster (Study M522101-J01) and 2 clinical studies in patients with herpes simplex (Studies M522101-J11 and M522101-J12), therefore, N-acetyl-β-D-glucosaminidase (NAG) and urine α1-microglobulin (α1-MG) were measured as urine markers of renal and renal tubular disorders in addition to regular renal function parameters (blood urea nitrogen and creatinine).

The percentage of subjects with abnormally increased NAG and urine α1-MG[26)] in the above 3 Japanese clinical studies is as shown in Table 28; the percentage in the amenamevir group tended to be higher than that in the VACV group. However, the increases in NAG or urine α1-MG were mostly transient and resolved without particular treatment in all the affected subjects except for 3 subjects in the amenamevir 200 mg group in whom the concerned event did not resolve. In addition, there were no adverse events suggestive of proximal renal tubular disorders such as polyuria and pollakiuria.

Based on the above, the effect of amenamevir on renal tubules is considered to be clinically insignificant.

25) Drug-like crystals were observed in urine or urinary sediment from 2 of 6 subjects in the amenamevir 1800 mg group in Study 15L-CL-002 (CTD 5.3.1.1-1) and from 6 of 8 subjects in the amenamevir 1200 mg group in Study 15L-CL-004 (CTD 5.3.3.3-2). The applicant explained that these crystals were observed only in specimens stored in a refrigerator but not observed in fresh urine specimens.
26) When the measured value (or adjusted value) falls within a range of the reference value at baseline, and any of the subsequent measured values (or adjusted value) exceeds; or when the measured value (or adjusted value) at baseline is above the reference value, and any of the subsequent measured values (or adjusted value) indicates aggravation from baseline.

Table 28. Subjects with increases in NAG or urine α1-MG in Study M522101-J01 and pooled data from 2 studies in patients with herpes simplex

	Patients with herpes zoster (Study M522101-J01)						Patients with herpes simplex (Studies M522101-J11 and M522101-J12)	
	Non-adjusted value			Adjusted value[a)]			Non-adjusted value	Adjusted value[a)]
	Amenamevir 400 mg (n = 249)	Amenamevir 200 mg (n = 252)	VACV (n = 249)	Amenamevir 400 mg (n = 249)	Amenamevir 200 mg (n = 252)	VACV (n = 249)	Amenamevir 200 mg (n = 580)	Amenamevir 200 mg (n = 580)
NAG increased	31 (12.4)	24 (9.5)	23 (9.2)	7 (2.8)	8 (3.2)	7 (2.8)	62 (10.7)	21 (3.6)
α1-MG urine increased	48 (19.3)	50 (19.8)	47 (18.9)	23 (9.2)	32 (12.7)	14 (5.6)	122 (21.0)	64 (11.0)

No. of subjects (%), a) Adjusted according to urine creatinine value

(b) Safety in patients with renal impairment

In foreign phase I study in subjects with renal impairment (Study 15L-CL-014), C_{max} of amenamevir was consistent irrespective of the degree of renal function. AUC_{inf}, on the other hand, tended to increase with the increasing severity of renal impairment [see Section 6.2.3.1]. AUC_{inf} (28.6 μg·h/mL) in subjects with severe renal impairment was still similar to AUC_{tau} (28.3 μg·h/mL) in healthy adult subjects who received amenamevir 1200 mg for 14 days in a foreign phase I study (Study 15L-CL-004) [see Section 6.2.1.4]. Because any of the adverse drug reactions in the amenamevir 1200 mg group in Study 15L-CL-004 was mild,[27)] raising no safety issues, the increased AUC_{inf} in subjects with severe renal impairment is considered to have no large clinical concern.

In addition, in the amenamevir 400 mg group in Japanese clinical studies in patients with herpes zoster (Studies 15L-CL-221 and M522101-J01), the incidence of adverse events and adverse drug reactions was 47.3% (113 of 239) and 13.0% (31 of 239), respectively, of subjects with normal renal function (creatinine clearance [CL_{cr}] ≥80 mL/min) and 53.5% (38 of 71) and 18.3% (13 of 71), respectively, of subjects with mild renal impairment (CL_{cr} ≥50 mL/min and <80 mL/min), respectively. No large differences were observed in the incidence of adverse events between subjects with normal renal function and subjects with mild renal impairment.

Based on the above, amenamevir in patients with renal impairment is unlikely to raise particular safety issues compared with patients without renal impairment, and thus the applicant considers it unnecessary to provide special cautions for patients with renal impairment. So far, however, amenamevir has been used only in patients with renal impairment with CL_{cr} ≥16.8 mL/min, and has not been used in patients with renal impairment with CL_{cr} <16.8 mL/min or patients with renal failure in need of dialysis. The above description will be included in the package insert to provide the concerned information.

PMDA's view:

At present, particular cautions for events related to renal disorder are unnecessary, because increases in NAG or α1-MG was observed in subjects receiving amenamevir in Japanese clinical studies, but most of the concerned events were transient and resolved without particular treatment; and there were no clinical findings suggestive of proximal renal tubular disorder.

In addition, although exposure to amenamevir in patients with renal impairment was suggested to increase with the increasing severity of the impairment, PMDA accepts the applicant's explanation that particular cautions for patients with renal impairment are unnecessary at present as described below:

- In the foreign phase I study in which the exposure to amenamevir was similar to that in subjects with severe renal impairment, no particular safety concerns were raised.
- In Japanese clinical studies, no adverse events specific to patients with mild renal impairment occurred.

[27)] In Study 15L-CL-004, adverse events occurred in 37.5% (3 of 8) of subjects in the amenamevir 200 mg group, 50.0% (4 of 8) of subjects in the amenamevir 400 mg group, 25.0% (2 of 8) of subjects in the amenamevir 800 mg group, 50.0% (4 of 8) of subjects in the amenamevir 1200 mg group, and 31.3% (5 of 16) of subjects in the placebo group. Adverse events reported in the amenamevir 1200 mg group included dry eye, abdominal pain, vomiting, sensation of heaviness, metrorrhagia, and pelvic pain in 1 subject each (including duplicate counting). A causal relationship to the study drug could not be ruled out for abdominal pain, sensation of heaviness, and pelvic pain, but all of them were mild. Neither serious adverse events nor adverse events leading to discontinuation occurred.

The applicant, however, should collect information on the safety of amenamevir in patients with renal impairment after the market launch, and provide the obtained information to healthcare professionals as appropriate, because experience with amenamevir in patients with renal impairment is limited.

7.R.2.3 Platelet count decreased

The applicant's explanation on effects on haematology including platelet count decreased in subjects receiving amenamevir:

In a foreign phase I study (Study 15L-CL-019, CTD 5.3.3.1-4), serious thrombocytopenia occurred in 1 subject. In the concerned subject, platelet count decreased (measured count, $13 \times 10^3/\mu L$) was reported on Day 21 of treatment with the study drug, and the count was further decreased to below the measurement sensitivity on Day 23, resulting in discontinuation of the study drug. No abnormalities were observed in the other haematology parameters, and this event was diagnosed as idiopathic thrombocytopenic purpura based on the pathological condition. Idiopathic thrombocytopenic purpura is an autoimmune disease, but known to develop rarely in response to drugs such as kinin, quinidine, and nonsteroidal anti-inflammatory drug (*J Thromb Haemost.* 2009;7:911-8). This event was considered unlikely to be attributable to amenamevir, because a possibility of idiopathic thrombocytopenic purpura related to ibuprofen orally taken before development of thrombocytopenia cannot be ruled out for this event, and detailed immunological investigation of this event did not show any clear result indicative of a causal relationship to amenamevir.

In Japanese clinical studies in patients with herpes zoster or herpes simplex, adverse events[28)] related to haematology occurred in 6.3% (20 of 317) of subjects in the amenamevir 400 mg group, 6.3% (21 of 332) of subjects in the amenamevir 200 mg group, 12.0% (9 of 75) of subjects in the amenamevir 100 mg group, and 5.0% (16 of 322) of subjects in the VACV group in patients with herpes zoster (pooled analysis of Studies 15L-CL-221 and M522101-J01); and in 10.9% (63 of 580) of subjects in the amenamevir 200 mg group and 3.8% (6 of 157) of subjects in the placebo group in patients with herpes simplex (pooled analysis of Studies M522101-J11 and M522101-J12). No large differences were observed in incidences of adverse events among dose groups, and there were no serious adverse events nor adverse events related to haematology leading to discontinuation. In addition, no adverse events related to platelet count decreased occurred in the amenamevir group.

In the phase III study in patients with herpes zoster (Study M522101-J01), 5.3% (13 of 247) of subjects in the amenamevir 400 mg group, 4.1% (10 of 246) of subjects in the amenamevir 200 mg group, and 5.4% (13 of 240) of subjects in the VACV group experienced platelet count decreased to less than the reference value ($14.0 \times 10^4/\mu L$) on any of the measurement days, but all such events were mild (Grade 1 or 2) or slight (milder than Grade 1).

In the other foreign and Japanese clinical studies, no serious adverse events related to haematology occurred. Based on data from Japanese clinical studies, the applicant considers that amenamevir is unlikely to raise safety concerns related to haematology including platelet count decreased.

PMDA's view:

At present, the applicant's explanation is acceptable that amenamevir is unlikely to raise particular safety concerns related to haematology including platelet count decreased, because serious thrombocytopenia (1 subject) of which a causal relationship to amenamevir could not be ruled out occurred in the foreign phase I study (Study 15L-CL-019), but the clinical course suggested that an effect of a concomitant drug potentially led to the above event; and no particular concerns were found in adverse events related to platelet count decreased or haematology in the other Japanese and foreign clinical studies. However, when new findings on events related to haematology such as platelet count decreased associated with amenamevir become available after the market launch, information should be provided appropriately to healthcare professionals.

7.R.2.4 Effect on cardiovascular system

The applicant's explanation on the effect of amenamevir on the cardiovascular system:

In the foreign phase I study (Study 15L-CL-019, CTD 5.3.3.1-4), serious pericarditis occurred in 1 subject. The concerned subject visited a clinic, complaining of chest tightness on the day following the

[28)] Adverse events classified into "Blood and lymphatic system disorders" under System Organ Class of the MedDRA/J or ones classified into "Investigations" under System Organ Class of the MedDRA/J and related to haematology

end of treatment with the study drug, and pericarditis was diagnosed based on electrocardiogram findings. Its relationship to amenamevir could not be ruled out, but the concerned event resolved.

In Japanese clinical studies in patients with herpes zoster or herpes simplex, adverse events[29)] related to the cardiovascular system occurred in 6.3% (20 of 317) of subjects in the amenamevir 400 mg group, 3.0% (10 of 332) of subjects in the amenamevir 200 mg group, 6.7% (5 of 75) of subjects in the amenamevir 100 mg group, and 2.8% (9 of 322) of subjects in the VACV group in patients with herpes zoster (pooled analysis of Studies 15L-CL-221 and M522101-J01); and in 3.4% (20 of 580) of subjects in the amenamevir 200 mg group and 3.8% (6 of 157) of subjects in the placebo group in patients with herpes simplex (pooled analysis of Studies M522101-J11 and M522101-J12). Most of the events, however, were mild. A serious adverse event of angina pectoris occurred in 1 subject (in the amenamevir 200 mg group in Study M522101-J01), but its causal relationship to amenamevir was ruled out, and the concerned event resolved.

Events related to electrocardiogram abnormal reported in patients with herpes zoster included electrocardiogram QT prolonged in 4 subjects in the amenamevir 400 mg group, 3 subjects in the amenamevir 200 mg group, and 1 subject in the VACV group; and electrocardiogram ST segment elevation in 1 subject in the amenamevir 400 mg group. Those events reported in patients with herpes simplex included electrocardiogram QT prolonged in 6 subjects in the amenamevir 200 mg group and 4 subjects in the placebo group; electrocardiogram QRS complex abnormal in 1 subject in the amenamevir 200 mg group; and electrocardiogram QRS complex prolonged in 1 subject in the amenamevir 200 mg group. In these subjects, however, no symptoms of arrhythmia were observed. Events related to arrhythmia reported in patients with herpes zoster included atrioventricular block first degree in 2 subjects and ventricular extrasystoles in 1 subject in the amenamevir 200 mg group. A causal relationship to amenamevir could not be ruled out for all events, but they were mild. In the other Japanese and foreign clinical studies, no serious adverse events in the cardiovascular system occurred.

Based on the above, although adverse events in the cardiovascular system occurred in clinical studies, most of them were mild, and the QT/QTc study (Study M522101-J22) has shown that amenamevir does not prolong QT/QTc interval [see Section 6.2.5], indicating that amenamevir is unlikely to raise safety concerns related to the cardiovascular system. The applicant, therefore, considered it unnecessary to provide particular cautions for the effect on the cardiovascular system at present.

PMDA's view:
The applicant's explanation is acceptable that amenamevir is unlikely to raise safety concerns related to the cardiovascular system in consideration of the following points, although serious pericarditis of which a causal relationship to amenamevir could not be ruled out occurred in 1 subject in the foreign phase I study (Study 15L-CL-019):

- The QT/QTc study has shown that amenamevir does not prolong QT/QTc interval.
- The adverse events in the cardiovascular system reported in Japanese clinical studies were mild or moderate.

However, when new findings on events related to the cardiovascular system associated with amenamevir become available after the market launch, information should be provided appropriately to healthcare professionals.

7.R.2.5 Elderly patients

The incidence of herpes zoster increases with aging (*J Int Med Res.* 2002;30:56-65, *Arch Intern Med.* 1995;155:1605-9, *BMC Infect Dis.* 2013;13:170), thus, the applicant explained the safety of amenamevir in the elderly as follows:
Table 29 shows the summary of the safety in the non-elderly (<65 years) and elderly (≥65 years) in Japanese clinical studies in patients with herpes zoster (pooled analysis of Studies 15L-CL-221 and M522101-J01). The incidence of adverse events tended to be higher in the elderly than in the non-elderly in the amenamevir group, but their severity and seriousness were similar between the elderly and non-elderly.

[29)] Adverse events classified into "Cardiac disorders" or "Vascular disorders" under System Organ Class of the MedDRA/J, ones classified into "Investigations" under System Organ Class of the MedDRA/J and related to cardiovascular system examination findings, or the other ones potentially related to the cardiovascular system

Table 29. Summary of the safety in the elderly and non-elderly in Japanese clinical studies in patients with herpes zoster

	<65 years				≥65 years			
	Amenamevir 400 mg (n = 221)	Amenamevir 200 mg (n = 238)	Amenamevir 100 mg (n = 51)	VACV (n = 234)	Amenamevir 400 mg (n = 96)	Amenamevir 200 mg (n = 94)	Amenamevir 100 mg (n = 24)	VACV (n = 88)
Adverse events	102 (46.2)	109 (45.8)	27 (52.9)	115 (49.1)	53 (55.2)	50 (53.2)	18 (75.0)	41 (46.6)
Adverse drug reactions	29 (13.1)	26 (10.9)	14 (27.5)	31 (13.2)	17 (17.7)	21 (22.3)	8 (33.3)	15 (17.0)
Deaths	0	0	0	0	0	0	0	0
Grade ≥3 adverse events[a)]	0	0	1 (2.0)	1 (0.4)	0	0	0	1 (1.1)
Serious adverse events	1 (0.5)	1 (0.4)	1 (2.0)	2 (0.9)	1 (1.0)	0	1 (4.2)	1 (1.1)
Adverse events leading to discontinuation	0	0	1 (2.0)	1 (0.4)	1 (1.0)	1 (1.1)	0	1 (1.1)

No. of subjects (%)

a) Adverse events assessed at Grade ≥3 in accordance with the "Criteria of Severity of Adverse Drug Reactions for Drugs, etc." (PAB/SD Notification No. 80 dated June 29, 1992)

Adverse events with a ≥5% higher incidence in the elderly than in the non-elderly in the amenamevir group included constipation (amenamevir 100 mg group; 2.0% [1 of 51] of the non-elderly subjects, 8.3% [2 of 24] of the elderly subjects), nasopharyngitis (amenamevir 100 mg group; 5.9% [3 of 51] of the non-elderly subjects, 12.5% [3 of 24] of the elderly subjects), NAG increased (amenamevir 100 mg group; 2.0% [1 of 51] of the non-elderly subjects, 8.3% [2 of 24] of the elderly subjects), α1-MG increased (amenamevir 100 mg group; 2.0% [1 of 51] of the non-elderly subjects, 8.3% [2 of 24] of the elderly subjects), and rhinitis allergic (amenamevir 100 mg group; 0% [0 of 51] of the non-elderly subjects, 8.3% [2 of 24] of the elderly subjects). All of the events were non-serious, and none of them led to discontinuation.

In general, renal function is known to be decreased with aging, but particular safety issues are considered unlikely to be raised in patients with decreased renal function [see Section 7.R.2.2]. The applicant, therefore, considers that amenamevir is unlikely to raise elderly-specific safety concerns.

PMDA's view:
In Japanese clinical studies, the incidence of adverse events tended to be higher in the elderly than in the non-elderly, but absence of clear differences was confirmed in reported adverse events between the elderly and non-elderly.

The prevalence of herpes zoster, however, is higher in the elderly than in non-elderly, and experience with amenamevir in the elderly is limited at present. Therefore, the safety information of amenamevir in the elderly should be collected after the market launch continuously.

7.R.3 Clinical positioning

The applicant's explanation on clinical positioning of amenamevir:
The phase III study has shown that amenamevir is effective as with VACV [see Section 7.R.1], and absence of particular safety concerns has been confirmed [see Section 7.R.2].

At present, oral preparations of ACV, VACV, and FCV are mainly used in treatment of herpes zoster in Japan. Because the mechanism of action of amenamevir is different from those of these existing drugs, the mechanism of development of resistance in viruses is also considered to be different. Amenamevir, therefore, is expected to be effective at a certain level even in patients with herpes zoster who have not sufficiently responded to the conventional drugs.

In addition, the incidence of herpes zoster is high in the elderly (*J Int Med Res.* 2002;30:56-65, *Arch Intern Med.* 1995;155:1605-9, *BMC Infect Dis.* 2013;13:170), and in general, CL_{cr} tends to decrease with aging. All of ACV, VACV, and FCV are excreted into urine, and thus dose reduction corresponding to the renal impairment on the basis of CL_{cr} is recommended. Amenamevir, on the other hand, does not require dose adjustment on the basis of CL_{cr} [see Section 7.R.2.2], and thus it can be used without consideration on the effect on renal function.

Based on the above, amenamevir is expected to be not only a new option in treatment of herpes zoster but also a drug available even for patients who have not sufficiently responded to the conventional drugs and who have renal impairment.

PMDA's view:
In consideration of the reviews in Sections 7.R.1 and 7.R.2, amenamevir can be a new option in treatment of herpes zoster.

7.R.4 Indications, and dosage and administration

Based on Sections 7.R.1 and 7.R.2 as well as the following review, PMDA has concluded that the indication can be specified as "herpes zoster," and the dosage and administration can be specified as "The usual adult dosage is 400 mg of amenamevir administered orally once daily after a meal." as proposed.

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

7.R.4.1 Treatment duration

The applicant's explanation on treatment duration of amenamevir:
In the clinical course of herpes zoster, VZV proliferates during new formation of rash, especially, blister (for 3-7 days in general) (*Comprehensive Handbook of Clinical Dermatology 15*. First edition. 2003;33-41, *J Am Acad Dermatol.* 2007;57:S130-5). Therefore, treatment with amenamevir should be continued during new formation of rash. In the phase III study, thus, treatment duration of amenamevir was 7 days, and as a result, the efficacy and safety of amenamevir 400 mg in patients with herpes zoster were confirmed [see Sections 7.R.1 and 7.R.2]. In patients with decreased immune function or patients in a severe pathological condition, the clinical symptoms may remain even after 7-day treatment (*Journal of Clinical Therapeutics & Medicines.* 2012;28:161-73), but the efficacy and safety of amenamevir administered to patients with herpes zoster for ≥8 days have not been investigated. The treatment duration of amenamevir, therefore, was 7 days, and the caution was to be provided to indicate switch to the other therapy for patients in whom the symptom does not resolve or is aggravated after 7-day treatment. For approved drugs in the same class (ACV, VACV, and FCV), the treatment duration for herpes zoster is also 7 days (Zovirax Tablets 200, etc., Package Insert [2015.2, ver. 14], Valtrex Tablets 500, etc., Package Insert [2014.11, ver. 13], Famvir Tablets 250 mg, Package Insert [2016.11, ver. 9]).

Based on data from Japanese clinical studies and status of drugs in the same class, PMDA considers it possible to accept the applicant's proposal that the treatment duration of amenamevir is 7 days, and the caution is to be provided to indicate switch to the other therapy for patients who have not responded to amenamevir sufficiently.

7.R.5 Post-marketing investigations

The applicant's explanation on plan of post-marketing investigations for amenamevir:
Specified use-results surveys in patients with herpes zoster

- Objective of survey: To collect information on the safety and efficacy in routine clinical use, and to conduct a follow-up survey for herpes zoster-related pain
- Number of patients to be included in the survey: 1000 patients
- Follow-up period: 12 months after the start of amenamevir administration. The follow-up may be finished when both skin symptom and pain disappear.
- Survey period: 3 years (planned registration period, 1.5 years after start of sales)

In addition, information on sensitivity to amenamevir is planned to be continuously collected from spontaneous reports, literature, presentations at academic meetings, etc. even after the market launch.

PMDA considers it necessary to collect information on the following points after the market launch:

- Efficacy of amenamevir in patients with herpes zoster who have received previously ACV, VACV, or FCV
- Safety of amenamevir in patients with hepatic impairment
- Safety of amenamevir in patients with renal impairment
- Safety and efficacy of amenamevir in elderly patients

The above conclusion of PMDA 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 a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, the applicant's self-inspection implemented after the application found that a part of records to be retained were missing at approximately half of the study sites in the phase II study (Study 15L-CL-221, CTD 5.3.5.1-1).

Concerning this finding, PMDA asked the applicant to explain their view on reliability of the concerned study data and actions.

The applicant explained their conclusion that reliability of the data obtained from the concerned study could not be ensured.

PMDA concluded that measures such as exclusion of the corresponding study data from the submitted application data should be taken before the review.

In addition, the applicant was found to have received before application a report from 1 study site that some of the records to be retained were missing, but have submitted the application data without any measure such as exclusion of the study data obtained from this site. PMDA notified the applicant of the concerned finding as a matter to be improved.

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

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, because some of the study sites were found to be non-conforming to the drug GCP, PMDA concluded that measures such as exclusion of data in the relevant subjects from the submitted application data should be taken before the review.

Matter no-conforming to the drug GCP
Study sites
- Defective retention of a part of source documents (medical records, etc.)

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

On the basis of the data submitted, PMDA has concluded that amenamevir has efficacy in the treatment of herpes zoster, and that amenamevir has acceptable safety in view of its benefits. Amenamevir is clinically meaningful because it offers a new therapeutic option to patients with herpes zoster.

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

Review Report (2)

May 8, 2017

Product Submitted for Approval

Brand Name	Amenalief Tab. 200 mg
Non-proprietary Name	Amenamevir
Applicant	Maruho Co., Ltd.
Date of Application	April 27, 2016

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 in the following. 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 on issues presented in the Review Report (1) [see Sections "7.R.1 Efficacy" and "7.R.4 Indications, and dosage and administration" of the Review Report (1)].

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

1.1 Safety

At the Expert Discussion, the expert advisors supported PMDA's conclusions on platelet count decreased and the effect on the cardiovascular system described in Section "7.R.2 Safety" of the Review Report (1). In addition to the supporting comments, the expert advisors made the following comments on PMDA's conclusion on the effect on renal function:

- In the phase III study (Study M522101-J01), incidences of abnormal increases in N-acetyl-β-D-glucosaminidase (NAG) and urine α1-microglobulin (α1-MG) were higher in subjects receiving amenamevir than in patients receiving valacyclovir (VACV) [see Section 7.R.2.2 of the Review Report (1)]. This suggests that amenamevir may affect renal function as with the existing drugs such as VACV. Therefore, information on incidence of renal impairment in patients receiving amenamevir should be collected after the market launch.

- Based on the currently available data, PMDA has concluded that there is no need to issue an alert for events related to renal disorders. This conclusion is appropriate, but the applicant should continue to investigate the necessity of dose adjustment according to renal function as done for the existing drugs such as acyclovir (ACV), VACV, and famciclovir (FCV).

- As described in Section "7.R.2.2 Effect on renal function" of the Review Report (1), no amenamevir-related safety concerns have been raised for patients with renal impairment. In the foreign phase I study (Study 15L-CL-014), however, exposure to amenamevir increased in patients with severe renal impairment, and thus amenamevir should be carefully administered to these patients. Therefore, patients with unknown renal function should be tested to determine their renal function before starting treatment with amenamevir.

PMDA's discussion based on comments from the Expert Discussion:

The effect of amenamevir on renal function:
In the phase III study (Study M522101-J01), the increases in NAG and urine α1-MG in the amenamevir group were mostly transient, but these events occurred more frequently in the amenamevir group than in the VACV group. This suggests that amenamevir may affect the kidneys. The applicant, therefore,

should include cautions for increases in NAG and urine α1-MG in the package insert, collect information on the effect of amenamevir on renal function after the market launch, and take appropriate measures such as information provision to healthcare professionals where necessary.

The safety in patients with renal impairment:
Dose adjustment according to renal function is probably unnecessary in view of the currently available data from Japanese and foreign clinical studies. The applicant should collect information on the safety of amenamevir in patients with renal impairment through post-marketing surveillance, and take appropriate measures such as information provision to healthcare professionals where necessary.

PMDA instructed the applicant to take actions described above. The applicant agreed.

1.2 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Section "7.R.5 Post-marketing investigations" of the Review Report (1). The expert advisors made the following comments, in addition to comments described in Section "1.1 Safety" of the Review Report (2):

- Safety data in elderly patients and patients with renal impairment should be collected adequately through the post-marketing surveillance.

- Amenamevir is expected to be used in combination with nonsteroidal anti-inflammatory drugs, some of which affect renal function. The applicant should therefore collect safety data in patients receiving amenamevir in combination with nonsteroidal anti-inflammatory drugs.

Based on comments from expert advisors and the review presented in Section "1.1 Safety" of the Review Report (2), PMDA considers that information on the following points should be collected in the post-marketing surveillance:

- Efficacy of amenamevir in patients with herpes zoster who have received prior treatment with ACV, VACV, or FCV

- Safety of amenamevir in patients with hepatic impairment

- Safety of amenamevir in patients with renal impairment

- Effect of amenamevir on renal function

- Safety and efficacy of amenamevir in elderly patients

To evaluate the safety of amenamevir in combination with other drugs, the applicant should collect information on concomitant drugs and on the safety of amenamevir in routine clinical use through the post-marketing surveillance, and appropriately inform healthcare professionals about new findings as they become available.

In addition, the applicant should continue to collect information on sensitivity to amenamevir from literature after the market launch, and appropriately inform healthcare professionals about new findings as they become available.

PMDA requested that the applicant investigate the above points. The applicant agreed, stating that the target sample size for the specified use-results survey was determined as 3000 to sufficiently investigate the above points in the post-marketing surveillance.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for amenamevir should include the safety and efficacy specifications presented in Table 30, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 31. PMDA thus accepted the outline of the specified use-results survey (draft) presented in Table 32.

Table 30. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
Not applicable	- Renal disorder - Events in the cardiovascular system - Platelet count decreased	Not applicable
Efficacy specification		
- Efficacy in routine clinical use		

Table 31. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
- Early post-marketing phase vigilance - Specified use-results surveys in patients with herpes zoster	- Early post-marketing phase vigilance

Table 32. Outline of specified use-results survey (draft)

Objective	To collect information on the safety and efficacy in routine clinical use, and to conduct a follow-up survey on postherpetic neuralgia
Survey method	Central registration system
Population	Patients receiving amenamevir for the treatment of herpes zoster
Survey period (observation period)	4 years (1 month, but if pain does not disappear 1 month after the first dose, up to 6 months to follow up postherpetic neuralgia)
Planned sample size	3000 patients
Main survey items	Characteristics of patients, use status of amenamevir, concomitant drugs and therapies, skin lesion and pain status at start of treatment with amenamevir, clinical course, general improvement of skin symptoms, adverse events, abnormal laboratory changes

2. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the indication and the dosage and administration shown below, with the following condition of approval. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product, and neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Herpes zoster

Dosage and Administration

The usual adult dosage is 400 mg of amenamevir administered orally once daily after a meal.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.