Report on the Deliberation Results

December 28, 2009

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

[Brand name]	Rapiacta 300 mg bag for intravenous drip infusion Rapiacta 150 mg vial for intravenous drip infusion
[Non-proprietary name]	Peramivir Hydrate (JAN*)
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	October 30, 2009

[Results of deliberation]
In the meeting held on December 26, 2009, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported 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, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

The dosage and administration statement of the package insert should be modified as follows:
"Usually, for adults, 300 mg of peramivir should be administered as a single intravenous infusion over at least 15 minutes.
For patients at high risk for severe influenza complications etc., 600 mg of peramivir should be administered as a single intravenous infusion over at least 15 minutes. Once-daily multiple doses of 600 mg may be administered according to the patient's symptoms.
The dosage should be reduced, as appropriate, according to the patient's age and symptoms."
(The underlined text represents addition.)

[Conditions for approval]

1. Collect post-marketing information on usage conditions and safety over a certain period of time, covering all patients treated with the product. Report the collected results to the regulatory authority periodically and take necessary action for the proper use of the product.

2. Report the results of Japanese and foreign surveillance of and information on peramivir-resistant influenza viruses to the regulatory authority, as required.

**Japanese Accepted Name (modified INN)*

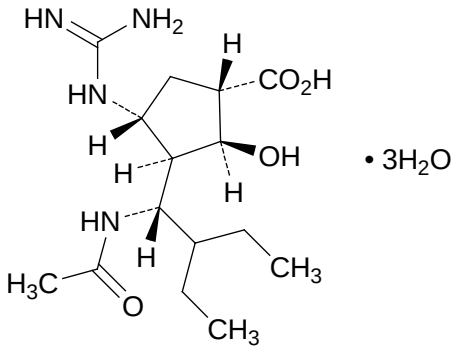
Review Report

December 16, 2009
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Rapiacta 300 mg bag for intravenous drip infusion (b) Rapiacta 150 mg vial for intravenous drip infusion
[Non-proprietary name]	Peramivir Hydrate
[Name of applicant]	Shionogi & Co., Ltd.
[Date of application]	October 30, 2009
[Dosage form/Strength]	(a) An injectable solution containing 349.4 mg of Peramivir Hydrate (300 mg as peramivir) per bag (b) An injectable solution containing 174.7 mg of Peramivir Hydrate (150 mg as peramivir) per vial
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{15}H_{28}N_4O_4 \cdot 3H_2O$

Molecular weight: 382.45

Chemical name:

(1*S*,2*S*,3*R*,4*R*)-3-[(1*S*)-1-(acetylamino)-2-ethylbutyl]-
4-guanidino-2-hydroxycyclopentanecarboxylic acid trihydrate

[Items warranting special mention]

Priority Review (Notification No. 1119-10 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 19, 2009)

[Reviewing office] Office of New Drug IV

Review Results

December 16, 2009

[Brand name]	(a) Rapiacta 300 mg bag for intravenous drip infusion (b) Rapiacta 150 mg vial for intravenous drip infusion
[Non-proprietary name]	Peramivir Hydrate
[Name of applicant]	Shionogi & Co., Ltd.
[Date of application]	October 30, 2009

[Results of review]

Based on the submitted data, the efficacy of peramivir against influenza A or B virus infection has been demonstrated and the safety of peramivir is acceptable in view of its observed benefits. It is necessary to collect post-marketing information on the efficacy of peramivir against some strains of influenza viruses with an amino acid substitution in neuraminidase (NA), e.g., H275Y mutant virus, and influenza B virus and the safety of multiple-dose peramivir.

Taking account of the Japanese and overseas situations surrounding influenza infections, e.g., the ongoing pandemic of novel influenza A (H1N1), and the clinical significance of the route of administration (i.e., intravenous infusion) of peramivir, it is necessary to identify usage conditions and collect safety information over a certain period of time, covering all patients treated with peramivir, in order to identify treated patients and usage conditions when peramivir has been made available to clinical practice, and take necessary action for the proper use of peramivir.

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

A prior assessment consultation was conducted on the product.

[Indication]

Influenza A or B virus infection

[Dosage and administration]

Usually, for adults, 300 mg of peramivir should be administered as a single intravenous infusion over at least 15 minutes.

For patients at high risk for serious influenza complications etc., 600 mg of peramivir should be administered as an intravenous infusion over at least 15 minutes. Once-daily multiple doses of 600 mg may be administered according to the patient's symptoms.

The dosage should be reduced, as appropriate, according to the patient's age and symptoms.

[Conditions for approval]

1. Collect post-marketing information on usage conditions and safety over a certain period of time, covering all patients treated with the product. Report the collected results to the regulatory authority periodically and take necessary action for the proper use of the product.

2. Report the results of Japanese and foreign surveillance of and information on peramivir-resistant influenza viruses to the regulatory authority, as required.

Review Report (1)

November 4, 2009

I. Product Submitted for Registration

[Brand name]	(a) Rapiacta 300 mg bag for intravenous drip infusion (b) Rapiacta 150 mg vial for intravenous drip infusion
[Non-proprietary name]	Peramivir Hydrate
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	October 30, 2009
[Dosage form/Strength]	(a) An injectable solution containing 349.4 mg of Peramivir Hydrate (300 mg as peramivir) per bag (b) An injectable solution containing 174.7 mg of Peramivir Hydrate (150 mg as peramivir) per vial
[Proposed indication]	Influenza A or B virus infection
[Proposed dosage and administration]	Usually, for adults, 300 mg of peramivir should be administered as a single intravenous infusion over at least 15 minutes. For patients at high risk for severe illness, 600 mg of peramivir may be administered once daily for up to 5 days. The dosage should be reduced as appropriate according to the patient's age and symptoms.

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

The data submitted in this application and the outline of review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Peramivir Hydrate (hereinafter, "peramivir") is a novel antiviral agent against influenza discovered by BioCryst Pharmaceuticals, Inc. (US-based BioCryst). By selectively inhibiting influenza A and B virus neuraminidase (NA), peramivir prevents the release of new virions from infected cells, thereby stopping virus replication indirectly.

In Japan, amantadine hydrochloride, zanamivir hydrate, and oseltamivir phosphate have been approved as antiviral agents against influenza. However, the following problems have been

identified: (a) amantadine hydrochloride can be used in limited patients as it has no anti-viral activity against influenza B virus and amantadine-resistant viruses occur frequently and (b) because zanamivir hydrate is an inhaled drug, it is difficult to administer the inhaled drug to children and the elderly who are unfamiliar with inhalation therapy. Regarding oseltamivir phosphate, oseltamivir-resistant influenza virus A (H1N1) harboring the H275Y mutation[1] has emerged in recent years and the spread of this influenza virus is of great concern to the global community. Also, since abnormal behavior leading to an accident, such as a fall, has been reported among pediatric patients receiving the drug, though causality is unknown, a precaution regarding the use of oseltamivir phosphate in pediatric patients[2] has been included in the package insert. Furthermore, in view of recent fears about a potential pandemic of highly pathogenic avian influenza A (H5N1) and the ongoing pandemic of novel influenza A (H1N1) virus infection, which was identified in the American Continent in April 2009 [novel influenza A (H1N1) virus], faster development of a novel antiviral agent against influenza is needed.

Rapiacta 150 mg vial for intravenous drip infusion and Rapiacta 300 mg bag for intravenous drip infusion (the product[3]) are preparations for intravenous infusion, which can be administered also to patients with medical conditions such as chronic respiratory disease or patients who have difficulty with an oral or inhaled medication due to severe influenza symptoms. In Japan, the development of peramivir as an intravenous infusion was initiated in [redacted] 20[redacted] and 2 phase I studies, 1 phase II study, and 2 phase III studies have been conducted to date. Because the phase III studies have confirmed the efficacy and safety of peramivir in the treatment of influenza A and B viral infections, the product has now been submitted for registration. On the other hand, outside of Japan, although the development of peramivir as an oral formulation was initiated by [redacted] in 19[redacted], the development of peramivir as an oral formulation was terminated because a phase III study failed to demonstrate adequate efficacy of peramivir in the treatment of acute influenza A and B viral infections. Then, peramivir was developed as an intramuscular formulation and as an intravenous infusion by US-based BioCryst. However, the development of peramivir as an intramuscular formulation was suspended because phase II studies of intramuscular peramivir (Studies BCX1812-211 and

[1] The mutation in NA of oseltamivir phosphate-resistant influenza virus A (H1N1) is referred to as "H275Y" based on the amino acid sequence of NA of influenza virus subtype H1N1 or "H274Y" according to N2 numbering based on the amino acid sequence of NA of influenza virus subtype H3N2. The mutation is called "H275Y" in this report.

[2] The WARNINGS section of the package insert for Tamiful capsules 75 and Tamiful dry syrup 3% states that "Although causality is unknown, there have been reports of abnormal behavior leading to an accident such as a fall after taking the drug among pediatric and adolescent patients ≥ 10 years of age. Therefore, as a rule, the use of the drug in patients of this age group should be withheld unless they are considered to be at high risk due to their concurrent or prior medical conditions etc. For children and adolescents, as a measure to prevent possible accidents, the following points should be explained to the patient/their family: after start of treatment with the drug, (1) abnormal behavior may occur and (2) the parent etc. should ensure that the child/adolescent is not left alone for at least 2 days when treated at home. Because there have also been reports of similar symptoms occurring in the setting of influenza encephalopathy etc., the above points should be explained."

[3] The drug product in vials was used in clinical studies.

BCX1812-212) failed to show a significant difference in the primary endpoint of the time to alleviation of influenza symptoms between peramivir and placebo and a phase III study (Study BCX1812-311) was prematurely terminated for changing the dose.[4] Meanwhile, 6 phase I studies and 1 phase II study of peramivir as an intravenous infusion have been conducted and a phase III study is currently under planning.

Peramivir has not been approved overseas as of November 2009.[5]

2. Data relating to quality

2.A. *Summary of the submitted data*

2.A.(1) Drug substance

2.A.(1).1) Characterization

(a) General properties

The determined physicochemical properties of the drug substance include description, solubility, hygroscopicity, thermal analysis, melting point, pH, dissociation constant, partition coefficient, optical rotation, isomerism, and crystalline polymorphism.

The drug substance is a white to pale yellow-brownish white powder. It is sparingly soluble in water, slightly soluble in methanol and in ethanol (99.5), and very slightly soluble in *N*,*N*-dimethylformamide. It is soluble in pH [redacted] buffer, sparingly soluble in pH [redacted] to [redacted] buffers, and sparingly soluble in [redacted]. Depending on [redacted], some [redacted] are observed, but the mass change is minimal and it is not hygroscopic. Its specific rotation is [redacted]° to [redacted]°. The drug substance has a very small 1-octanol/water partition coefficient at 20°C to 25°C.

(b) Structure determination

The chemical structure of the drug substance is supported by elementary analysis, mass spectrometry, ultraviolet spectroscopy, infrared spectrophotometry, nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), and X-ray crystallography.

(c) Crystalline polymorphism

Besides the trihydrate form of the drug substance (the desired crystalline form, Form 1), two

[4] As Study BCX1812-211 showed that peramivir 300 mg had an enhanced anti-viral effect compared to 150 mg and was well-tolerated, BioCryst considered that it was necessary to evaluate the efficacy and safety of peramivir at a higher dose and terminated Study BCX1812-311 at a peramivir dose of 300 mg and then conducted Study BCX1812-212 at a peramivir dose of 600 mg.

[5] In the US, the Food and Drug Administration (FDA) issued an Emergency Use Authorization as of October 23, 2009.

polymorphs (Form 3 and Form 4) and [redacted], [redacted] (Form 2) have been identified.

Although the Form 1 (the desired crystalline form) and Form 2 ([redacted]) of the drug substance may form upon [redacted] in the current manufacturing process, Form 1 and Form 2 were able to be distinguished by any of infrared spectrum, water content, X-ray powder diffraction pattern, and photomicrograph. In manufacture, formed crystals are to be identified by [redacted] and furthermore, [redacted] of [redacted] is to be measured to confirm that the obtained crystals are peramivir trihydrate.

2.A.(1).2) Manufacturing process

The drug substance, "Peramivir Hydrate" is produced using [redacted] ([redacted]) as starting material through the manufacturing process comprising 4 steps. The drug substance is manufactured by [redacted] (Switzerland) and [redacted] (the US). The differences in the manufacturing process between [redacted] and [redacted] are [redacted] of [redacted] used in Step [redacted] and Step [redacted] and [redacted] of [redacted] in Step [redacted]. The drug substances ("Peramivir Hydrate") obtained from the manufacturing processes of the two companies met all acceptance criteria as described in "3.2.S.4.5 Justification of specification" and stability studies of the drug substances of the two companies also showed no changes in all attributes tested as described in "3.2.S.7 Stability."

Step 1: Warm a mixture of [redacted] and [redacted]. Drop [redacted] at [redacted]°C and agitate at [redacted]°C for [redacted] minutes. Wash with [redacted] to obtain [redacted] of [redacted] [2].

Step 2: Drop [redacted] of [2] obtained in Step 1 in [redacted] and agitate and then separate the liquids. Cool the obtained [redacted], add [redacted], and adjust [redacted] to [redacted]. Add [redacted], agitate for [redacted] minutes, and obtain [redacted] of [redacted] [3].

Step 3: Add [redacted] of [3] obtained in Step 2 to [redacted]. Add [redacted], adjust [redacted], agitate, and cause crystals to form. Centrifuge the formed crystals and wash with [redacted]. Dry the crystals to obtain [redacted] [4].

Step 4: [redacted] of [4] to be used at the initiation of Step 4 and if [redacted][6] [redacted]% or [redacted][5] [redacted]%, after completing Step [redacted], [redacted] Step [redacted]. Dissolve a mixture of [4] obtained in Step 3, [redacted], and

[6] [redacted]: [redacted] of "Peramivir Hydrate" drug substance

[redacted] and filtrate the mixture with [redacted]. Concentrate the filtrate, drop a solution obtained by [redacted] in [redacted], and concentrate. After agitation under [redacted], cool slowly and confirm that the formed crystals are [redacted]. After further cooling and agitation, centrifuge the obtained crystals and wash with [redacted]. Dry the crystals to obtain the drug substance “Peramivir Hydrate” [5].

(a) Controls of critical steps and intermediates

In the manufacture of the drug substance, Steps [redacted] to [redacted] are controlled as [redacted] critical steps. [redacted], used as [redacted] in Step [redacted], has been defined as a critical process intermediate.

(b) Manufacturing process development

The manufacturing process of the drug substance during the development phase is classified according to the synthetic route into two methods: Method [redacted] and Method [redacted]. According to how to [redacted] and how to [redacted] for [redacted], the Method [redacted] is further divided into three methods: Method [redacted], Method [redacted], and Method [redacted]. The current manufacturing process of the drug substance is [redacted] method.

Summary of Method [redacted]

	Method [redacted]	Method [redacted]	Method [redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

(c) Container closure system

The drug substance is to be packaged in double-layer polyethylene bags further placed in polyethylene drums with lids.

2.A.(1).3) Control of drug substance

The drug substance specifications were established on the basis of the data from a total of 6 lots, i.e. 3 commercial scale lots each of the drug substances produced by [redacted] and [redacted].

The proposed specifications for the drug substance include description (appearance), identification (infrared spectrum), purity (heavy metals, [redacted], related substances, [redacted], residual solvents), pH, water content, residue on ignition, bacterial endotoxins, and strength (assay).

(a) Reference standard

The proposed specifications for reference material include description (appearance),

identification (infrared spectrum, nuclear magnetic resonance spectrum), purity (related substances, [redacted], residual solvents), water content, residue on ignition, and purity.

2.A.(1).4) Stability of drug substance

Long-term testing and accelerated testing of the drug substance were conducted using 3 commercial-scale lots each at [redacted] and [redacted]. Stress testing and light exposure testing were conducted at Shionogi & Co., Ltd. The main storage conditions and testing frequency in the stability studies were as shown below.

Long-term testing and accelerated testing conducted by [redacted]

Study	Temperature	Humidity	Light	Storage package	Testing frequency
Long-term testing	30°C	65%RH	Protected from light	Double-layer [redacted] polyethylene bag + [redacted] polyethylene drum	0, 3, 6, 9, 12, 18, 24 (at submission), 36, 48, 60 months
Accelerated testing	40°C	75%RH	Protected from light	〃	0, 1, 2, 3, 6 months

Long-term testing and accelerated testing conducted by [redacted]

Study	Temperature	Humidity	Light	Storage package	Testing frequency
Long-term testing	30°C	65%RH	Protected from light	[redacted] polyethylene bag + [redacted] polyethylene bag + [redacted] polyethylene drum	0, 1, 2, 3, 6, 9, 12 (at submission), 18, 24, 36, 48, 60 months
Accelerated testing	40°C	75%RH	Protected from light	〃	0, 1, 2, 3, 6 months

Stress testing

Study		Temperature	Humidity	Light	Storage package	Testing frequency
Stress testing	Temperature	[redacted]°C	—	[redacted]	[redacted]	0, [redacted], [redacted] months
	Humidity	[redacted]°C	[redacted]%RH	[redacted]	[redacted]	
		[redacted]°C	[redacted]%RH	[redacted]	[redacted]	
	Light	25°C	—	D65 lamp	petri dish + polyvinylidene chloride film	0, 1.2 million lx·hr, [redacted] lx·hr (≥ 200 W·h/m^2)
		25°C	—	D65 lamp	petri dish + polyvinylidene chloride film + aluminum foil	0, 1.2 million lx·hr, [redacted] lx·hr (≥ 200 W·h/m^2)

(a) [redacted]

Under the long-term condition, [redacted] in [redacted] was observed, but there was no trend towards increases in related substances. There were no changes over time in other attributes tested after [redacted] months of storage compared to the initial time point (0 month).

Under the accelerated condition, there were no changes over time for all attributes tested after 6 months of storage compared to the initial time point (0 month).

(b) [redacted]

Under the long-term condition, [redacted] in [redacted] and [redacted] was observed, but there was no trend towards increases in related substances. There were no changes in other attributes tested after [redacted] months of storage compared to the initial time point (0 month).

Under the accelerated condition, there were no changes in all attributes tested after 6 months of storage compared to the initial time point (0 month).

(c) Stress testing and light exposure testing

Under the stress condition (temperature), there were no changes in all attributes tested after [redacted] months of storage compared to the initial time point (0 month).

Under the stress condition (humidity), there were no changes in all attributes tested after [redacted] months of storage compared to the initial time point (0 month).

Under the stress condition (light), [redacted] in [redacted] was observed both when exposed to 1.2 million lx·hr and to [redacted] lx·hr of light. [redacted] in [redacted] was observed also for concurrent dark controls. Thus, the applicant explained that this was not due to the effect of light, but attributable to [redacted] resulting from [redacted] (about [redacted]%RH) in a photostability testing apparatus.

Based on the above, the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003) was applied to this product application, and the retest period of 3 years, which is 12 months beyond the period of 24 months covered by the long-term stability data, has been proposed. The retest period will be extended using data generated from the ongoing long-term stability studies.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product

Rapiacta 300 mg bag for intravenous drip infusion (the drug product in bags) is a solution for intravenous infusion containing 300 mg of peramivir (349.4 mg as Peramivir Hydrate) per bag (60 mL).

Rapiacta 150 mg vial for intravenous drip infusion (the drug product in vials) is a solution for intravenous infusion containing 150 mg of peramivir (174.7 mg as Peramivir Hydrate) per vial (15 mL).

The compositions of the drug products in bags and in vials are as shown below. The drug product in vials used in phase III studies was identical in composition and formulation to the proposed commercial drug product. In clinical studies, the required volume was withdrawn from the vial and diluted in isotonic sodium chloride solution as appropriate before administration.

		Drug product in vials	Drug product in bags
Component	Component function	Amount (mg)	Amount (mg)
Peramivir Hydrate	Active ingredient	174.7	349.4
Sodium chloride	Isotonizing agent	135.0	540.0
Water for injection	Solvent	q.s.	q.s.
Total		15 mL	60 mL
Fill volume per container (including overages)		[redacted] mL	[redacted] mL

Drug substance: Peramivir Hydrate

2.A.(2).2)-1 Manufacturing process (the drug product in bags)

The drug product is produced through the manufacturing process comprising the following 6 steps and the manufacturing site will be [redacted].

Step 1: Dissolution, Step 2: Filtration, Step 3: Filling and Sealing, Step 4: Sterilization,
Step 5: Labeling and Packaging, Step 6: Testing and Storage

(a) Controls of critical steps and intermediates

In the manufacture of the drug product, Steps [redacted], [redacted], and [redacted] have been defined as critical process steps.

(b) Container closure system

The container closure system for the drug product is a polypropylene soft bag with [redacted] rubber stopper. The secondary packaging is a film with [redacted] (consisting of [redacted], [redacted], and [redacted]).

2.A.(2).2)-2 Manufacturing process (the drug product in vials)

The drug product is produced through the manufacturing process comprising the following 5 steps and the manufacturing site will be [redacted].

Step 1: Dissolution, Step 2: Sterile filtration, Step 3: Filling and Sealing,
Step 4: Labeling and Packaging, Step 5: Testing and Storage

(a) Controls of critical steps and intermediates

In the manufacture of the drug product, Steps [redacted], [redacted], and [redacted] have been defined as critical process steps.

(b) Container closure system

The container closure system for the drug product is a 20-mL colorless glass vial with a rubber closure for aqueous infusions and a cap.

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include description (appearance), identification (infrared spectrum), osmotic pressure ratio, pH, purity (Related Substance A), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility (membrane filtration method), and strength (assay).

2.A.(2).4) Stability of drug product

Pivotal stability studies submitted in the application were conducted using 3 pilot scale lots each of the drug products in bags and in vials. The main storage conditions and testing frequency in the stability studies were as shown below.

Stability studies of drug product in bags

Study	Temperature	Humidity	Light	Storage package	Testing frequency
Long-term testing	25°C	[redacted]%RH	Protected from light	polypropylene bag + vacuum-deposited aluminum pillow bag	0, 3, 6 (at submission), 9, 12, 18, 24, 36 months
Accelerated testing	40°C	[redacted]%RH	Protected from light		0, 3, 6 months
Light exposure testing	25°C	—	D65 lamp	polypropylene bag	0, 1.2 million lx·hr ($\geq$ 200 W·h/m^2)

Stability studies of drug product in vials

Study	Temperature	Humidity	Light	Storage package	Testing frequency
Long-term testing	25°C	60%RH	Protected from light	colorless glass vial + carton (inverted storage)	0, 3, 6 (at submission), 9, 12, 18, 24, 36 months
Accelerated testing	40°C	75%RH	Protected from light		0, 3, 6 months
Light exposure testing	25°C	—	D65 lamp	colorless glass vial (inverted storage)	0, 1.2 million lx·hr ($\geq$ 200 W·h/m^2)

(a) Drug product in bags

Under the long-term condition, the bag's mass was decreased over time and the percent

decrease was about [redacted]% after 6 months of storage. There were no changes from the initial timepoint (0 month) for other attributes tested. The long-term stability study up to 36 months is currently ongoing.

Under the accelerated condition, the level of Related Substance A that is formed in the sterilization process during the manufacture of the drug product [redacted] over time to reach [redacted]% at 6 months, which was a [redacted]% [redacted] from the initial time point (0 month). The bag's mass was decreased over time and the mass change was about [redacted]%.

Under the stress condition (light), the mass change was about [redacted]%. There were no changes in other attributes tested after light exposure.

Based on the above, a shelf life of 6 months, which is covered by the long-term stability data, has been proposed for the drug product in bags. The shelf life will be extended using data generated from the ongoing long-term stability study.

(b) Drug product in vials

Under the long-term condition, [redacted] tended to [redacted] slightly, but there were no changes from the initial timepoint (0 month) for other attributes tested. The long-term stability study up to 36 months is currently ongoing.

Under the accelerated condition, [redacted] tended to [redacted] slightly. Related Substance A was detected after [redacted] months of storage and the level of Related Substance A was < [redacted]% at [redacted] months of storage.

Under the stress condition (light), [redacted] tended to [redacted] slightly, but there were no changes in other attributes tested after light exposure.

Based on the above, a shelf life of 6 months covered by the long-term stability data has been proposed for the drug product in vials. The shelf life will be extended using data generated from the ongoing long-term stability study.

2.B. *Outline of the review by PMDA*

As a result of the following reviews, PMDA concluded as follows:

Although no compatibility study of the product has been conducted [see 2.B.(4) Incompatibility], the submitted data indicate that the quality of the product is appropriately

controlled by other attributes.

2.B.(1) Drug substance specifications

Concerning system suitability for [redacted], PMDA asked the applicant to review the number of times the test is repeated to test the system repeatability. The applicant reestablished it so as to ensure the appropriate precision of analysis system and PMDA accepted it.

2.B.(2) Manufacturing process for the drug substance

PMDA asked the applicant to describe control parameters and control values for starting material, a critical intermediate, and raw materials in the registration application for appropriate control. The applicant described them appropriately and PMDA accepted it.

2.B.(3) Shelf life for the drug product

A shelf life of 6 months has been proposed for both the drug product in bags and the drug product in vials based on the long-term stability data up to the time of regulatory submission and the applicant will continue the stability studies for up to 3 years. Twelve-month stability data will become available in January 2010 for the drug product in vials and in February 2010 for the drug product in bags.

PMDA concluded as follows:

Taking account of the social situation surrounding influenza viral infections, e.g. a pandemic of novel influenza A (H1N1) [see 1. Origin or history of discovery and usage conditions in foreign countries etc.], the medical need for early distribution of peramivir to medical practices is high with a view to offering a new treatment option for influenza viral infections. Also, the long-term and accelerated stability data suggest that a major quality problem is unlikely to occur. Therefore, the proposed shelf life of 6 months for the drug product is acceptable.

2.B.(4) Incompatibility

PMDA asked the applicant to explain the incompatibility of peramivir and the need to provide a caution.

The applicant responded as follows:

Because both the drug product in bags and the drug product in vials can be administered without dilution, no specific preparation procedure or particular caution regarding the preparation procedure and incompatibility is required. No compatibility study has been conducted so far, but in view of the possibility that peramivir may be mixed with other drugs, a compatibility study is

under planning.

PMDA considers that a compatibility study should have been conducted, as the drug product in a bag may be administered into an existing fluid infusion line through the Y-site. Therefore, PMDA instructed the applicant to provide a caution in the package insert, etc. that compatibility with other drugs is unknown at present, conduct a compatibility study promptly, and provide the information on the obtained results to medical practice.

The applicant responded as follows:
It will be cautioned appropriately in the package insert, etc. that compatibility with other drugs is unknown. A planned compatibility study is scheduled to be completed by the end of February 2010, but will be undertaken as soon as possible. Interim data will be reviewed as appropriate and if any safety problem is identified, safety measures will be considered promptly. When the results of this study become available, whether or not there is a safety problem etc. will be determined and necessary action will be taken, such as, by revising the "Precautions" section of the package insert. Thus, a caution and information will be provided to medical practice.

PMDA accepted the above response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A. *Summary of the submitted data*

As the evaluation data, the results from 30 primary pharmacodynamic studies and 6 safety pharmacology studies were submitted in the application. As the reference data, the results from 1 primary pharmacodynamic study were submitted.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* antiviral activity

(a) Inhibitory activity against seasonal influenza virus neuraminidases (NAs)【4.2.1.1-01 - 4.2.1.1-04】

Influenza A (H1N1, H3N2) and B virus (laboratory strains and clinical isolates) NAs were mixed with each investigational product and the NA inhibitory activity of each investigational product [the concentration of investigational product required for 50% inhibition of enzyme activity (inhibitory concentration 50%: IC_{50}), where the enzyme activity in the absence of

investigational product is taken as 100%] was determined by the assay of NA activity using fetuin as substrate (*Bull WHO* 1973;48:199-202). As a result, the IC_{50} values of peramivir, oseltamivir carboxylate,[7] and zanamivir for influenza A virus (11 strains) NAs were 0.54 to 11, 1.0 to 14, and 2.0 to 14 (nmol/L), respectively. The IC_{50} values of peramivir, oseltamivir carboxylate, and zanamivir for influenza B virus (5 strains) NAs were 6.8 to 17, 28 to 79, and 14 to 40 (nmol/L), respectively.

Influenza A (H1N1, H2N2, H3N2) and B virus (laboratory strains and clinical isolates) NAs were mixed with each investigational product and the NA inhibitory activity of each investigational product was determined by enzyme activity assay using a fluorogenic substrate [2'-(4-Methylumbelliferyl)-α-D-*N*-acetylneuraminic acid sodium salt hydrate (MUNANA)] (*Anal Biochem* 1979; 94 (2): 287-296). The results were as shown below.

Influenza virus NA inhibitory activity

	Type	Subtype	No. of strains	IC_{50} (nmol/L)		
				Peramivir	Oseltamivir carboxylate	Zanamivir
Laboratory strains	A	H1N1	10	0.31-0.94	0.94-1.61	1.24-3.21[1)]
	A	H2N2	3	1.39-1.77	0.82-1.04	4.72-6.42
	A	H3N2	8	0.98-1.52	0.66-1.16	4.14-9.07[2)]
Clinical isolates	A	H1N1	6	0.48-0.68	0.87-1.31	1.73 -1.90[3)]
	A	H3N2	15	0.72-1.72	0.34-1.11	2.80 -5.05[4)]
Laboratory strains	B	-	8	0.40-3.41	1.47-6.07	8.31-10.2[5)]
Clinical isolates	B	-	12	1.37-54.2[7)]	5.55-18.0	7.12-13.7[6)]

Mean IC_{50} was calculated using the results from 3 or 2 independent experiments and each experiment was performed in duplicate or triplicate.
For the B/Kanagawa/3/76 strain only, 1 of 3 experiments was performed in singlicate.
1) Data from 8 strains, 2) Data from 7 strains, 3) Data from 4 strains, 4) Data from 11 strains, 5) Data from 4 strains, 6) Data from 10 strains
7) The IC_{50} was 1.37 to 4.26 nmol/L for 11 strains among the strains tested and the IC_{50} was 54.2 nmol/L for the remaining 1 strain. The applicant discussed that the strain with an IC_{50} of 54.2 nmol/L (B/kadoma/19/2007) contained the H136Y and N221K mutations. The H136Y mutation was a very rare one.

(b) Inhibitory activity against neuraminidases (NAs) of various subtypes【4.2.1.1-04】

Influenza A virus NAs of different subtypes (N1-N9) were mixed with each investigational product and the NA inhibitory activity of each investigational product was determined by enzyme activity assay using MUNANA. As a result, the IC_{50} values of peramivir and oseltamivir carboxylate for the NA subtypes tested were 0.24 to 1.18 and 0.86 to 3.38 (nmol/L), respectively.

[7] The active form of oseltamivir phosphate

(c) Selectivity of NA inhibitory activity of peramivir【4.2.1.1-05 - 07】

Bacterial (*Arthrobacter ureafaciens*, *Streptococcus pneumoniae*, *Vibrio cholerae*) NAs were mixed with each investigational product and the NA inhibitory activity of each investigational product was determined by enzyme activity assay using MUNANA. As a result, the IC_{50} values of peramivir and oseltamivir carboxylate were 24.8 to > 1000 and 10.7 to 277.4 (μmol/L), respectively. On the other hand, the IC_{50} values of peramivir and oseltamivir carboxylate for a positive control (influenza virus B/Hong Kong/5/72) were 0.00111 and 0.00541 (μmol/L), respectively.

Four types of human sialidases, NEU1 to NEU4, which cleave the terminal sialic acid residues from glycoproteins on the cell surface, were mixed with peramivir or a positive control compound [2,3-Dehydro-2-deoxy-*N*-acetylneuaminic acid (DANA)] and the NA inhibitory activity of peramivir or DANA was determined by enzyme activity assay using MUNANA as a subtrate for NEU1, NEU2, and NEU4 and ganglioside GM3 as a substrate for NEU3. As a result, the IC_{50} values of peramivir and DANA for NEU1 to NEU4 were 150 to > 5000 and 3.4 to 160 (μmol/L), respectively. On the other hand, since the IC_{50} of peramivir for influenza virus (A/PR/8/34) sialidase was 0.00025 (μmol/L), the applicant discussed that peramivir has high selectivity for influenza virus NA.

Main receptors, ion channels, and transporters of humans, rats, etc. (a total of 63 different receptors, ion channels, or transporters) were mixed with ^{3}H- or ^{125}I-labeled ligands and peramivir and then radioactivity was determined to assess the inhibition of ligand binding to different receptors, ion channels, and transporters by peramivir. As a result, peramivir did not cause apparent inhibition of ligand binding to any receptor, ion channel, or transporter even at a concentration as high as ≥ 1000-fold the IC_{50} of peramivir for influenza virus NA (10 μmol/L).

(d) *In vitro* virus replication inhibition【4.2.1.1-08 - 11】

RPMI2650 cells (human nasal septum-derived cell line) were inoculated with influenza A (H1N1, H3N2) and B virus strains and incubated for 2 days in the presence or absence of peramivir. The collected culture supernatants were inoculated into Madin-Darby canine kidney cells (MDCK cells) and 50% tissue culture infectious doses ($TCID_{50}$) of viruses in the supernatants were determined by measuring cytopathic effect (CPE) after 3- to 4-day incubation. The 90% inhibitory concentration (IC_{90}) was defined as the drug concentration reducing $TCID_{50}$ to 10% of the control value. The results were as shown below.

Inhibition of influenza A and B virus release by peramivir

Type	Subtype	Viral strain	IC_{90} (nmol/L)		
			Peramivir	Oseltamivir carboxylate	Zanamivir
A	H1N1	A/Kadoma/3/2006	57	> 1000 [a)]	1000 [b)]
	H1N1	2007-268	56	> 1000 [a)]	460
	H1N1	A/SendaiH/1049/2007	180	560 [c)]	>1000 [a)]
	H1N1	A/SendaiH/K133/2007	13	710 [b)]	310
	H3N2	A/Kadoma/1/2005	72	81 [b)]	>1000 [a)]
	H3N2	A/SendaiH/F494/2007	1800 [b)]	> 5000 [a)]	>5000 [a)]
B	-	B/Kadoma/1/2005	320	280 [c)]	170
	-	B/Kadoma/2/2005	490	900 [c)]	130 [b)]
	-	B/SendaiH/43/2007	150	940 [c)]	420
	-	B/SendaiH/F646/2007	110	> 1000 [a)]	470 [b)]

Mean IC_{90} was calculated using the results from 3 independent experiments.

a) IC_{90} values obtained in 3 experiments were all above the tested concentration range.
b) Mean IC_{90} from 2 experiments. IC_{90} value obtained in the remaining 1 experiment was above the tested concentration range.
c) IC_{90} value from 1 experiment. IC_{90} values obtained in the other 2 experiments were above the tested concentration range.

MDCK cells were inoculated with influenza A (H1N1, H3N2) and B virus strains (laboratory strains and clinical isolates) and incubated for 1 hour. Then, an agar medium containing each investigational product was overlayed and the MDCK cells were incubated for 3 days. After the cells were stained with neutral red, the inhibition of plaque formation by each investigational product [50% effective concentration (EC_{50})] was measured based on the number and size of plaques formed. The results were as shown below.

Inhibition of plaque formation by influenza A and B viruses

			EC_{50} (nmol/L)		
Type	Subtype	Viral strain	Peramivir	Oseltamivir carboxylate	Zanamivir
Laboratory strains					
A	H1N1	A/WS/33	15	60	37
A	H1N1	A/PR/8/34	0.93	140	5.8
A	H3N2	A/Victoria/3/75	0.36	0.78	4.6
Clinical isolates					
A	H1N1	A/Kadoma/3/06	0.48	7.5	13
A	H1N1	A/Sendai-H/K133/2007	17	200	130
A	H1N1	A/Sendai-H/1049/2007	18	360	75
A	H3N2	A/Kadoma/1/04	0.16	11	25
A	H3N2	A/Kadoma/1/05 a)	0.39	5.3	12
A	H3N2	A/Kadoma/1/06	0.064	260	3.6
A	H3N2	A/Sendai-H/F494/2007 a)	1.9	32	59
Laboratory strains					
B	-	B/Lee/40	25	31	21
B	-	B/Maryland/1/59	26	42	29
Clinical isolates					
B	-	B/Kadoma/2/05	4.8	47	7.9
B	-	B/Sendai-H/0040/2007	120	720	150
B	-	B/2007-297	52	30	7.9

Mean EC_{50} was calculated using the results from 3 independent experiments.

a) Assessed based on the area calculated from the measured diameters of plaques

Influenza A (H1N1, H3N2) and B virus solutions were mixed with each investigational product and MDCK cells and incubated for 3 days and then added with WST reagent. After 2-hour incubation, sodium dodecyl sulfate solution was added and absorbance (at 450 nm) was measured to assess the inhibition of influenza virus replication by peramivir. As a result, the EC_{50} values of peramivir and oseltamivir carboxylate for influenza A (H1N1, H3N2) and B virus strains (a total of 6 strains) were 0.013 to 1.739 and 0.045 to 4.324 (μmol/L), respectively.

3.(i).A.(1).2) *In vivo* antiviral activity

(a) Improvement of survival in mice infected with influenza A virus【4.2.1.1-12 - 15】

Mice were intranasally inoculated with influenza virus A/WS/33 (H1N1) [inoculum dose, 5×10^3 $TCID_{50}$/mouse] and at 48 hours after inoculation, single intravenous doses of 0.3, 1, 3, and 10 mg/kg of peramivir were administered, 0.3, 1, 3, and 10 mg/kg/day of oseltamivir phosphate were orally administered twice daily (BID) for 5 days, or a single oral dose of 10 mg/kg of oseltamivir phosphate was administered. The survival rates and 50% effective doses (ED_{50}) on Day 14 after inoculation were calculated. The survival rate was significantly improved in the peramivir 3 and 10 mg/kg groups and in the oseltamivir phosphate 3 and 10 mg/kg/day

(multiple oral doses) groups compared to the vehicle group ($P < 0.05$, Fisher's exact test). On the other hand, there was no significant improvement in the survival rate in the oseltamivir phosphate (a single oral dose) group compared to the vehicle group. The ED_{50} values of peramivir, oseltamivir phosphate (multiple oral doses), and oseltamivir phosphate (a single oral dose) were 1.5, 3.0, and > 10 [mg/kg (/day)], respectively.

Likewise, immediately after mice were intranasally inoculated with influenza virus A/PR/8/34 (H1N1) [inoculum dose, 4×10^2 $TCID_{50}$/mouse], A/Kumamoto/Y5/67 (H2N2) [inoculum dose, 2.5×10^2 $TCID_{50}$/mouse], or A/Victoria/3/75 (H3N2) [inoculum dose, 7.5×10^2 $TCID_{50}$/mouse], single intravenous doses of 0.1, 0.3, 1, 3, and 10 mg/kg of peramivir were administered, 0.3, 1, 3, 10, and 30 mg/kg/day of oseltamivir phosphate were orally administered BID for 5 days, or single oral doses of 10 and 30 mg/kg of oseltamivir phosphate were administered. The survival rates and ED_{50} values on Day 14 after inoculation were calculated.

As a result, the survival rate was significantly improved in the peramivir ≥ 1 mg/kg groups[8] and in the oseltamivir phosphate (multiple oral doses) ≥ 3 mg/kg/day groups, compared to the vehicle group for all strains of influenza virus ($P < 0.05$, Fisher's exact test). On the other hand, there was no significant improvement in the survival rate in the oseltamivir phosphate (a single oral dose) 10 mg/kg group[9] compared to the vehicle group. The ED_{50} values of peramivir, oseltamivir phosphate (multiple oral doses), and oseltamivir phosphate (a single oral dose) were 0.4 to 0.9, 3.4 to 6.7, and > 30 [mg/kg (/day)], respectively.

(b) Improvement of survival in mice infected with influenza B virus【4.2.1.1-16 - 17】

Immediately after mice were intranasally inoculated with influenza virus B/Maryland/1/59 (inoculum dose, 2.5×10^2 $TCID_{50}$/mouse), single intravenous doses of 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg of peramivir were administered, 0.3, 1, 3, and 10 mg/kg/day of oseltamivir phosphate were orally administered BID for 5 days, or a single oral dose of 10 mg/kg of oseltamivir phosphate was administered. The survival rates and ED_{50} values on Day 14 after inoculation were calculated. The survival rate was significantly improved in the peramivir ≥ 0.3 mg/kg groups and in the oseltamivir phosphate ≥ 1 mg/kg/day (multiple oral doses) groups compared to the vehicle group ($P < 0.05$, Fisher's exact test). On the other hand, there was no significant improvement in the survival rate in the oseltamivir phosphate (a single oral dose) group compared to the vehicle group. The ED_{50} values of peramivir, oseltamivir phosphate (multiple

[8] For influenza virus A/PR/8/34, the survival rate was significantly improved also in the peramivir 0.3 mg/kg group, compared to the vehicle group ($P < 0.05$, Fisher's exact test).

[9] For A/Victoria/3/75 only among the three influenza virus strains tested, the survival rate was significantly improved in the oseltamivir phosphate (a single oral dose) 30 mg/kg group, compared to the vehicle group ($P < 0.05$, Fisher's exact test).

oral doses), and oseltamivir phosphate (a single oral dose) were 0.1, 1.7, and > 10 [mg/kg (/day)], respectively.

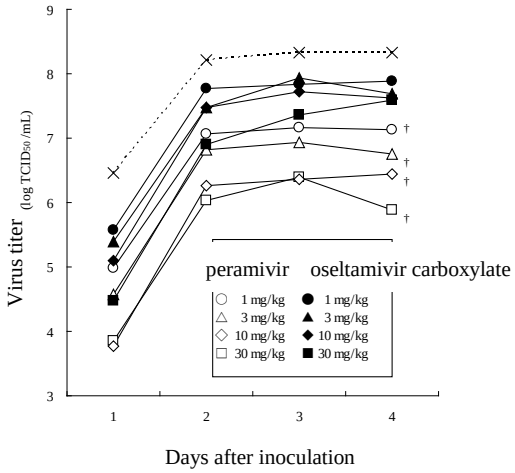
Immediately after mice were intranasally inoculated with influenza virus B/Lee/40 (inoculum dose, 4×10^2 $TCID_{50}$/mouse), single intravenous doses of 0.1, 0.3, 1, 3, and 10 mg/kg of peramivir were administered, 0.3, 1, 3, 10, and 30 mg/kg/day of oseltamivir phosphate were orally administered BID for 5 days, or single oral doses of 10 and 30 mg/kg of oseltamivir phosphate were administered. The survival rates and ED_{50} values on Day 14 after inoculation were calculated. The survival rate was significantly improved in the peramivir ≥ 1 mg/kg groups and in the oseltamivir phosphate ≥ 10 mg/kg/day (multiple oral doses) groups, compared to the vehicle group ($P < 0.05$, Fisher's exact test). On the other hand, there was no significant improvement in the survival rate in the oseltamivir phosphate (a single oral dose) groups, compared to the vehicle group. The ED_{50} values of peramivir, oseltamivir phosphate (multiple oral doses), and oseltamivir phosphate (a single oral dose) were 1.0, 7.8, and > 30 [mg/kg (/day)], respectively.

(c) Therapeutic time window study in mice infected with influenza A virus【4.2.1.1-18】

Mice were intranasally inoculated with influenza virus A/WS/33 (H1N1) [inoculum dose, 5×10^3 $TCID_{50}$/mouse] and at 24, 48, 60, 72, 84, and 96 hours post-infection, a single intravenous dose of 10 mg/kg of peramivir was administered or 10 mg/kg/day of oseltamivir phosphate was orally administered BID for 5 days. The survival rates on Day 14 after inoculation were calculated. As a result, the survival rate was significantly improved in the peramivir and oseltamivir phosphate groups compared to the vehicle group when therapy began within 72 hours and 60 hours after inoculation, respectively ($P < 0.05$, Fisher's exact test). When therapy began 72 hours after inoculation in the oseltamivir phosphate group, all mice died.

(d) Inhibition of lung virus replication in mice infected with influenza A virus【4.2.1.1-19】

Immediately after mice were intranasally inoculated with influenza virus A/Victoria/3/75 (H3N2) [inoculum dose, 7.5×10^2 $TCID_{50}$/mouse], single intravenous doses of 1, 3, 10, and 30 mg/kg of peramivir and oseltamivir carboxylate were administered. Lung homogenate supernatants collected on Days 1, 2, 3, and 4 after inoculation (virus solutions) were inoculated into MDCK cells and after 3-day incubation, $TCID_{50}$ was determined by measuring CPE. The results were as shown below.



Lung virus titer over time in a lethal murine model of infection
The data points in the graph represent mean lung virus titers from 3 mice.
The dashed line in the graph represents virus titer over time in the vehicle group.
IC_{50} of peramivir: 0.98 nmol/L
IC_{50} of oseltamivir carboxylate: 0.66 nmol/L
†: $P < 0.01$ (comparison with oseltamivir carboxylate at the same dose, two-way ANOVA using day of measurement and dose as explanatory variables)

The survival rate on Day 14 after inoculation was significantly improved in the peramivir ≥ 1 mg/kg groups compared to the vehicle group ($P < 0.05$, Fisher's exact test). On the other hand, there was no significant improvement in the survival rate in all oseltamivir carboxylate groups, compared to the vehicle group.

(e) Dissociation rate of peramivir from NA【4.2.1.1-20, Reference data 4.2.1.1-31】

Each investigational product was mixed with recombinant N9 NA and a reaction buffer for 1 hour and each investigational product-NA complex was purified through columns (Bio-Spin 6). Recovery of NA activity over time was assessed by measuring enzyme activity in the purified samples using MUNANA. As a result, at 4 hours after substrate addition, peramivir-NA complex and oseltamivir carboxylate-NA complex showed 6.2 ± 0.7% and 78.0 ± 7.2% (mean ± SD), respectively, of the NA activity.

Recovery of NA activity over a longer period of time was assessed in the same manner. As a result, at 24 hours after substrate addition, peramivir-NA complex and oseltamivir carboxylate-NA complex showed 30.8% and 93.7%, respectively, of the NA activity.

Based on the above results, the applicant discussed that a substantial difference in the rate of dissociation from NA between the two drugs contributes to the more potent inhibition of virus replication in mouse lung by a single intravenous dose of peramivir, compared to oseltamivir carboxylate.

(f) Pharmacokinetic parameters affecting therapeutic effect in mice【4.2.1.1-21 - 22, 4.2.2.2-06】

Mice were intranasally inoculated with influenza A/WS/33 (H1N1) virus (inoculum dose, 5×10^3 $TCID_{50}$/mouse) and at 48 hours after inoculation, 0.25, 0.5, 1, 2, 4, and 8 mg/kg of peramivir were intravenously administered as single doses, two divided doses every 6 hours (48 and 54 hours after inoculation), or four divided doses every 3 hours (48, 51, 54, and 57 hours after inoculation) (a total of 18 patterns). The survival rates on Day 14 after inoculation were calculated. The results are as shown below. Higher survival rate was associated with increasing dosing frequency at the same dose per administration and almost all mice receiving ≥ 2 mg/kg survived regardless of dosing frequency.

Pharmacodynamic effect of peramivir intravenously administered as single doses, two divided doses, or four divided doses

Test drug	Dosing frequency (Dosing interval)	Total dose (mg/kg) [Dose per administration (mg/kg)]	Survivors[b)]/Total
Peramivir	Single dose	0.25	0/10
		0.5	1/10
		1	4/10
		2	9/10
		4	10/10
		8	10/10
	Two divided doses (6 hours)	0.25 [0.125]	3/10
		0.5 [0.25]	2/10
		1 [0.5]	6/10
		2 [1]	10/10
		4 [2]	10/10
		8 [4]	10/10
	Four divided doses (3 hours)	0.25 [0.0625]	1/10
		0.5 [0.125]	2/10
		1 [0.25]	5/10
		2 [0.5]	10/10
		4 [1]	10/10
		8 [2]	10/10
Vehicle (saline)	4 doses (3 hours)	0	0/20

IC_{50} of peramivir, 0.31 nmol/L

In order to analyze the correlation between the survival rate improvement in mice infected with

A/WS/33 and the pharmacokinetic parameters of peramivir [maximum plasma concentration (C_{max}[10] [peramivir 0.4 mg/kg, 2.11 μg/mL; 2 mg/kg, 9.07 μg/mL; 10 mg/kg, 60.5 μg/mL]), area under plasma concentration-time curve (AUC [peramivir 0.4 mg/kg, 0.516 μg·hr/mL; 2 mg/kg, 2.51 μg·hr/mL; 10 mg/kg, 14.5 μg·hr/mL]), the duration of concentrations above the 95% inhibitory concentration against the NA of A/WS/33 strain ($T > IC_{95}$)], the data were fitted to a logistic curve and Akaike's Information Criterion (*Budapest*; *Akademiai Kiado* 1973;267-281) was used. As a result, the Akaike's Information Criterion values were 150.643, 113.750, and 123.684 for C_{max}, AUC, and $T > IC_{95}$, respectively. The applicant discussed that although a correlation of C_{max} or $T > IC_{95}$ with the survival rate improvement in mice was not denied, AUC was most correlated.

(g) Activity against oseltamivir phosphate-resistant influenza viruses【4.2.1.1-23 - 25】

Influenza A (H1N1) virus (a clinical isolate) NA (with the H275Y mutation) was mixed with each investigational product and the NA inhibitory activity of each investigational product was determined by enzyme activity assay using MUNANA. As a result, the NA IC_{50} values (mean) of peramivir, oseltamivir carboxylate, and zanamivir for human influenza A (H1N1) virus with the H275Y mutation were 19.9 to 88.9 (35.4), 112 to 378 (225), and 1.25 to 2.63 (1.73) nmol/L, respectively. On the other hand, the NA IC_{50} values (mean) of peramivir, oseltamivir carboxylate, and zanamivir for human influenza A (H1N1) virus without the H275Y mutation were 0.597 to 1.56 (0.968), 1.11 to 3.89 (1.91), and 1.37 to 9.48 (4.01) nmol/L, respectively.

The NAs of recombinant influenza viruses A/PR/8/34 and A/WSN/33 carrying the H275Y NA mutation were mixed with each investigational product and the NA inhibitory activity of each investigational product was determined by enzyme activity assay using MUNANA. Fold resistance (FR) was calculated by dividing the IC_{50} value for the mutant NA by that for the wildtype NA. The results were as shown below.

Change in peramivir susceptibility due to H275Y mutation

Recombinant virus				Peramivir		Oseltamivir carboxylate		Zanamivir	
Type	Subtype	Viral strain	NA mutation	IC_{50} (nmol/L)	FR	IC_{50} (nmol/L)	FR	IC_{50} (nmol/L)	FR
A	H1N1	A/PR/8/34	-	0.545	-	1.35	-	1.17	-
A	H1N1	A/PR/8/34	H275Y	21.5	39	150	111	1.65	1
A	H1N1	A/WSN/33	-	0.615	-	1.13	-	1.39	-
A	H1N1	A/WSN/33	H275Y	18.2	30	152	134	1.60	1

Mean IC_{50} was calculated using the results from 3 independent experiments.

[10] C_{max} was the extrapolated plasma concentration at time 0 in this study.

Immediately after mice were intranasally inoculated with a recombinant influenza virus with the H275Y mutation (A/PR/8/34), single intravenous doses of 1, 3, 10, 30, and 100 mg/kg of peramivir were administered or 1, 3, 10, 30, and 100 mg/kg/day of oseltamivir phosphate were orally administered BID for 5 days. The survival rates and ED_{50} values in mice on Day 14 after inoculation were calculated. As a result, the survival rate was significantly improved in the peramivir ≥ 3 mg/kg groups and in the oseltamivir phosphate ≥ 30 mg/kg/day groups, compared to the vehicle group ($P < 0.05$, Fisher's exact test). On the other hand, the survival rate was significantly improved with 3 and 10 mg/kg of peramivir, compared to the same doses of oseltamivir phosphate ($P < 0.05$, Fisher's exact test).

(h) Activity against viruses with known NA inhibitor-resistant mutations【4.2.1.1-26】

The NAs of various influenza viruses with NA mutations were mixed with each investigational product and the NA inhibitory activity and FR of each investigational product were determined by enzyme activity assay using MUNANA. As a result, H275Y in the N1 subtype, E119G, E119A, E119D, D151V, D151A, D151N, D151G, and R292K in the N2 subtype, and R152K, D198Y, I222T, H275Y, and R371K in the B type conferred a ≥ 10-fold reduction in susceptibility to peramivir. Of these mutations, I222T and H275Y in the B type showed a ≥ 10-fold reduction in susceptibility to peramivir alone. N294S in the N1 subtype, E119V and N294S in the N2 subtype, and S250G in the B type were associated with a reduction in susceptibility to oseltamivir carboxylate or zanamivir, but were still sensitive to peramivir.

(i) Activity against influenza A virus in immunosuppressed mice【4.2.1.1-27】

Mice treated intraperitoneally with cyclophosphamide (CPA) were intranasally inoculated with influenza virus A/WS/33 (H1N1) [inoculum dose, 2.0×10^4 $TCID_{50}$/mouse] and the investigational drugs were given to the animals at 48 hours after inoculation. The survival rates and ED_{50} values on Day 21 after inoculation were calculated. The results were as shown below. Mice untreated with CPA were administered the investigational products and studied in the same manner. As a result, the ED_{50} values of peramivir and oseltamivir phosphate were 2.4 and 2.8, respectively, and the survival rate was significantly improved with both investigational products at ≥ 3 mg/kg, compared to the vehicle group ($P < 0.05$, Fisher's exact test).

Therapeutic effect in a lethal immunosuppressed murine model

Investigational product (Administration method)	Dose [mg/kg (/day)]		
		Survivors/Total	ED_{50} [mg/kg (/day)]
Vehicle [0.5% methylcellulose] (multiple oral doses BID for 5 days)	-	0/20	-
Peramivir (single intravenous dose)	1	0/10	> 100
	3	0/10	
	10	0/10	
	30	0/10	
	100	4/10 *	
Peramivir (multiple intravenous doses QD for 5 days)	1	0/10	6.8
	3	1/9	
	10	8/10 *,#,†	
	30	9/10 *,#,†	
	100	10/10 *,#	
Oseltamivir phosphate (multiple oral doses BID for 5 days)	1	0/10	78.6
	3	0/10	
	10	0/10	
	30	0/10	
	100	7/10 *	

IC_{50} of peramivir: 0.31 nmol/L, IC_{50} of oseltamivir carboxylate, 0.98 nmol/L
a) Treated intraperitoneally with CPA 50 mg/kg (Days -1, 3, 7 of virus infection)
QD: once daily
*: $P < 0.05$ (comparison with vehicle by Fisher's exact test)
#: $P < 0.05$ (comparison with a single dose of peramivir at the same dose by Fisher's exact test)
†: $P < 0.05$ (comparison with oseltamivir phosphate at the same dose by Fisher's exact test)

(j) Activity against highly pathogenic avian influenza viruses【4.2.1.1-28 - 30】

Highly pathogenic avian influenza virus (H5N1, H7N1, H7N7) NAs were mixed with each investigational product and the NA inhibitory activity of each investigational product was determined by the assay of NA activity using fetuin as substrate. The results were as shown below.

NA inhibitory activity for highly pathogenic avian influenza viruses

Viral strain	Subtype	IC_{50} (nmol/L)		
		Peramivir	Oseltamivir carboxylate	Zanamivir
A/Hong Kong/483/97	H5N1	0.23	5.00	1.38
A/chicken/Yamaguchi/7/04	H5N1	0.40	6.18	0.99
A/whooper swan/Mongolia/3/05	H5N1	0.39	8.07	1.77
A/chicken/Italy/99	H7N1	0.26	7.63	1.72
A/chicken/Netherlands/03	H7N7	0.12	1.10 a)	4.88

Mean IC_{50} was calculated using the results from 3 independent experiments.
a) Mean IC_{50} value from 2 experiments

MDCK cells were inoculated with highly pathogenic avian influenza viruses and incubated for 2 days in the presence or absence of peramivir. The collected culture supernatants were inoculated into new MDCK cells and $TCID_{50}$ of viruses in the supernatants were determined by measuring CPE after 3-day incubation. IC_{90} was defined as the drug concentration reducing $TCID_{50}$ to 10%

of the control value. The results were as shown below.

Inhibition of highly pathogenic avian influenza virus replication

Viral strain	Subtype	IC_{90} (nmol/L)		
		Peramivir	Oseltamivir carboxylate	Zanamivir
A/Hong Kong/483/97	H5N1	1.7	20	37
A/chicken/Yamaguchi/7/04	H5N1	1.0	5.2	2.5
A/whooper swan/Mongolia/3/05	H5N1	1.1	6.9	7.9
A/chicken/Italy/99	H7N1	7.5	54	31
A/chicken/Netherlands/03	H7N7	2.6	1.8	11

Mean IC_{90} was calculated from 3 independent experiments.

Immediately after mice were intranasally inoculated with highly pathogenic avian influenza virus A/Hong Kong/483/97 (H5N1) [inoculum dose, 100 EID_{50} (50% egg-infective dose)/mouse], the investigational products were administered. The survival rates on Day 14 after inoculation were calculated. The results were as shown below.

Therapeutic effect in a lethal murine model of infection with A/Hong Kong/483/97 strain

Investigational product (Administration method)	Dose [mg/kg (/day)]	Survivors/Total
Vehicle [0.5% methylcellulose] (repeated oral doses BID for 5 days)	-	0/20
Peramivir (single intravenous dose)	10	6/10 *
	30	7/10 *
Peramivir (repeated intravenous doses BID for 5 days)	10	9/10 *,#,†
	30	10/10 *,†
Oseltamivir phosphate (repeated oral doses BID for 5 days)	10	3/10 *
	30	7/10 *
Zanamivir (repeated intravenous doses BID for 5 days)	10	1/10
	30	5/10 *

*: $P < 0.05$ (comparison with vehicle by Fisher's exact test)
#: $P < 0.05$ (comparison with oseltamivir phosphate at the same dose by Fisher's exact test)
†: $P < 0.05$ (comparison with zanamivir at the same dose by Fisher's exact test)

3.(i).A.(2) Secondary pharmacodynamics

No secondary pharmacodynamic data was submitted in this application.

3.(i).A.(3) Safety pharmacology

Six studies conducted for this application and their results are summarized in the table below.

	Type of study	Species	Mode of administration	Doses of peramivir [a)] (mg/kg)	Gender and No. per group	Noteworthy findings
Central nervous system	Effects on general symptoms and behavior	Rats	Intravenous	20, 50, 100	6 males/group	Increased landing foot splay at 100 mg/kg[11]
Respiratory system	Effects on respiratory rate, tidal volume, and minute ventilation	Rats	Intravenous	20, 50, 100	8 males/group	No effects
	Effects on airway resistance, dynamic lung compliance, blood pressure, and heart rate	Guinea pigs	Intravenous	1, 3, 10	8 males/group	No effects
Cardiovascular system	Effects on blood pressure, heart rate, and ECG parameters	Monkeys	Intravenous	30, 60	4 males/group	No effects
	Effects on papillary muscle action potential	Guinea pigs	Applied to the nutrient solution	3, 30, 300 μmol/L	5 males/group	No effects
	Effects on myocardial ion channels	HEK293 cells expressing hERG channels	Applied to the perfusate	300 μmol/L	3/group	No effects

a) Unless otherwise specified, single dose administration.

3.(i).B. *Outline of the review by PMDA*

3.(i).B.(1) NA inhibitory activity for clinical isolates from clinical studies

PMDA asked the applicant to tabulate the NA inhibitory activity of each investigational product for clinical isolates from clinical studies conducted for this application [a Japanese phase II study (Study [redacted]22T0621), a multiregional phase III study conducted in East Asian countries (Japan, Korea, Taiwan) (Study [redacted]15T0631), a Japanese phase III study in high-risk patients with influenza viral infections (Study [redacted]16T0632)] and the applicant submitted the following table.

[11] 【Note by PMDA】 The applicant discussed increased landing foot splay in the peramivir 100 mg/kg group as follows: There were no effects on other general symptoms and behavior and the baseline value of landing foot splay in the 100 mg/kg group was higher than that in the control group. When 200 mg/kg of peramivir was intravenously administered in two divided doses to rats (the second dose was administered at 4 hours after the first dose, the dose per administration was 100 mg/kg), C_0 after the first dose was 455 μg/mL. When a single intravenous dose of 800 mg of peramivir, the highest dose, was administered to Japanese healthy adult male subjects in a clinical study, the plasma pharmacokinetic parameter of peramivir (C_{max}) was 85.2 μg/mL. Therefore, peramivir is unlikely to affect the central nervous system in clinical use.

			Japanese phase II study (ITTI)	Multiregional phase III study (ITTI)	Japanese phase III study (PPS)
A/H1[1)]	N		158	593	16
	IC_{50} Mean (SD) (nmol/L)	Peramivir	1.41 (0.961)	22.2 (4.37)	21.8 (2.12)
		Oseltamivir	2.56 (3.56)	87.7 (16.4)	87.1 (16.1)
		Zanamivir	3.62 (2.23)	1.35 (0.178)	1.42 (0.0987)
A/H3	N		69	323	13
	IC_{50} Mean (SD) (nmol/L)	Peramivir	1.48 (0.403)	0.828 (0.172)	0.849 (0.0990)
		Oseltamivir	1.07 (0.321)	0.632 (0.168)	0.705 (0.110)
		Zanamivir	3.44 (0.680)	1.97 (0.370)	2.11 (0.162)
A/-	N		6	46	1
	IC_{50} Mean (SD) (nmol/L)	Peramivir	1.15 (0.428)	14.1 (9.98)	23.2 (-)
		Oseltamivir	1.73 (0.715)	56.6 (43.7)	68.4 (-)
		Zanamivir	3.04 (1.23)	1.54 (0.336)	1.46 (-)
B	N		3	70	3
	IC_{50} Mean (SD) (nmol/L)	Peramivir	2.81 (0.190)	3.51 (0.386)	3.48 (0.0610)
		Oseltamivir	8.17 (0.819)	16.5 (2.50)	18.1 (2.53)
		Zanamivir	9.05 (0.758)	9.74 (1.10)	9.43 (0.304)
A/H1 and A/H3	N		0	1	0
	IC_{50} Mean (SD) (nmol/L)	Peramivir	-	1.79 (-)	-
		Oseltamivir	-	0.957 (-)	-
		Zanamivir	-	1.57 (-)	-

1) 【Note by PMDA】Among seasonal influenza viruses isolated at screening in the multiregional phase III and Japanese phase III studies (studied period, 20[redacted]-20[redacted] season), 99.8% (483 of 484 specimens) and 100% (12 of 12 specimens), respectively, of the sequenced specimens had the H275Y mutation. On the other hand, in the Japanese phase II study, although the presence or absence of the H275Y mutation was not determined for all clinical isolates, because only 1 (IC_{50}, 44.0 nmol/L) of 8 specimens with high IC_{50} values had the H275Y mutation, the applicant inferred that the incidence of the H275Y mutant virus was low during the season of the Japanese phase II study (studied period, 20[redacted]-20[redacted] season).

PMDA considers as follows:

(a) Influenza A viruses

It was confirmed that the NA IC_{50} values of peramivir for clinical isolates of influenza A/H3 virus from the Japanese phase II study and the multiregional phase III study were similar. On the other hand, most of the clinical isolates of influenza A/H1 virus from the multiregional phase III study were oseltamivir-resistant strains with the H275Y mutation and these isolates exhibited high NA IC_{50} for not only oseltamivir, but also peramivir. There is a concern that the antiviral effect of peramivir against strains with amino acid substitutions including oseltamivir-resistant strains with the H275Y mutation may be reduced. Therefore, although it is necessary to collect post-marketing information on the effect against resistant strains etc., based on the submitted documents and the above data submitted by the applicant, peramivir is expected to be effective against influenza A viruses.

(b) Influenza B viruses

It was confirmed that the NA IC_{50} values of peramivir for clinical isolates of influenza B virus from the Japanese phase II study and the multiregional phase III study were similar.

According to the submitted documents, the IC_{50} of peramivir was high for 1 strain with the H136Y mutation among the strains of influenza B virus. However, as this mutation is not found

among the 707 clinical isolates of influenza B virus registered from 2000 to date with the Influenza Virus Resource, an influenza virus database provided by the National Center for Biotechnology Information (NCBI) of the National Institute of Health (NIH) (the US), the applicant discussed that it is a very rare mutation. Although it is necessary to collect post-marketing information on peramivir resistance, based on the submitted documents and the above data submitted by the applicant, peramivir is expected to be effective against influenza B viruses.

The clinical efficacy of peramivir against influenza A and B viruses will be discussed in "4.(iii).B.(1) Efficacy."

3.(i).B.(2) Cross-resistance between peramivir and other antiviral agents agains influenza (NA inhibitors)

PMDA asked the applicant to discuss cross-resistance between peramivir and other antiviral agents against influenza (NA inhibitors).

The applicant responded as follows:

Peramivir is a compound that incorporates the hydrophobic group from oseltamivir carboxylate and the guanidino group from zanamivir. Because peramivir has both the hydrophobic group that interacts with the hydrophobic region of the NA active site and the guanidino group that is electrically bound to acidic amino acids within the NA active site, an amino acid substitution affecting the binding of one group to the NA active site is unlikely to markedly affect the NA inhibitory activity of peramivir as long as the other group remains tightly bound to the NA active site. In a non-clinical pharmacology study, N294S in the N1 subtype, E119V and N294S in the N2 subtype, and S250G in the B type were associated with a reduction in susceptibility to oseltamivir carboxylate or zanamivir, while the mutants were still sensitive to peramivir and no cross-resistance was observed. On the other hand, there were also mutants highly or moderately resistant to all of the 3 inhibitors, i.e.. cross-resistant mutants.

Therefore, while the possibility of cross-resistance between peramivir and other NA inhibitors can not be ruled out, the degree of resistance varied. Although the NA inhibitory activity of peramivir may be reduced depending on the types of amino acid substitutions in NA, peramivir has a different resistance profile from the existing NA inhibitors, which will be a useful characteristic in the event of the emergence of a new mutant.

PMDA considers as follows:

Although the submitted data suggest the degree of peramivir resistance is not always similar to the degree of resistance to other NA inhibitors, the possibility of cross-resistance between peramivir and other NA inhibitors can not be ruled out and there is a concern about the emergence of a resistant virus associated with the use of peramivir. Therefore, it is necessary to continue to collect post-marketing information on peramivir resistance.

3.(i).B.(3) Antiviral activity against novel influenza A (H1N1) virus

The Center of Disease Control and Prevention (CDC) assessed the NA inhibitory activities (IC_{50}) of peramivir and other influenza antiviral agents for novel influenza A (H1N1) virus. As a result, the IC_{50} values of peramivir, oseltamivir phosphate, and zanamivir were 0.06 to 0.26, 0.28 to 1.41, and 0.30 to 1.34 nmol/L, respectively. Also, it was reported that the IC_{50} of peramivir against novel influenza A (H1N1) virus (0.16 nmol/L) is similar to the IC_{50} against seasonal influenza virus (0.56 nmol/L) (*MMWR* 2009 May 1; 58(16): 433-435).

PMDA asked the applicant to explain about any ongoing study and any new finding on novel influenza A (H1N1) virus. The applicant responded that although there is no ongoing study or new information at present, a strain of novel influenza A (H1N1) virus will be obtained in future to confirm the efficacy of peramivir against it.

PMDA considers as follows:

According to the CDC's report, the NA inhibitory activity of peramivir is similar for novel and seasonal influenza A (H1N1) viruses. Thus, peramivir is expected to be effective against novel influenza A (H1N1) virus. However, because the clinical efficacy of peramivir has not been evaluated to date, it is necessary to continue to collect information.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A *Summary of the submitted data*

The pharmacokinetics of ^{14}C-labeled or unlabeled peramivir in mice, rats, rabbits, and monkeys were determined. In studies using peramivir and ^{14}C-labeled peramivir, radioactivity levels in biological samples were determined by liquid scintillation counter, the tissue distribution of radioactivity was determined by quantitative whole-body autoradiography, metabolites in plasma, urine, bile, and feces were analyzed by radio-high performance liquid chromatography (Radio-HPLC), liquid chromatography/tandem mass spectrometry, and high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS), and plasma peramivir concentrations were measured by LC/MS/MS. Doses and concentrations in *in vitro* studies are expressed in terms of peramivir.

3.(ii).A.(1) Absorption【4.2.2.2-01 - 07】

Following a single intravenous dose of 10 mg/kg of ^{14}C-labeled peramivir in male rats and female monkeys, the AUC_{inf}[12] values of plasma radioactivity and peramivir were 23.4 ± 3.5 μg eq.·hr/mL and 23.8 ± 2.7 μg·hr/mL, respectively, in rats and 65.0 ± 33.4 μg eq.·hr/mL and 63.0 ± 32.2 μg·hr/mL (mean ± SD), respectively, in monkeys. The extrapolated plasma concentrations at time 0 (C_0) were 37.5 ± 9.1 μg eq. /mL and 35.6 ± 8.1 μg /mL (mean ± SD), respectively, in rats and 68.3 ± 15.0 μg eq. /mL and 66.9 ± 15.7 μg /mL (mean ± SD), respectively, in monkeys. The results showed that the AUC_{inf} and C_0 values of plasma radioactivity were almost comparable to those of plasma peramivir. This was also true for other pharmacokinetic parameters [elimination half-life ($t_{1/2}$), total body clearance (CL_{tot})] and plasma concentration over time.

Following single intravenous administration of peramivir at doses of 3 to 30 mg/kg to male rats and female monkeys and at doses of 0.4 to 50 mg/kg to noninfected female mice, the pharmacokinetic parameter (AUC_{inf}) was linear[13] over the dose range tested in rats and monkeys and over the dose range of 0.4 to 10 mg/kg in mice. The plasma pharmacokinetic parameter after single intravenous administration of peramivir at 0.4 to 10 mg/kg in female mice 2 days after inoculation with influenza A virus was almost comparable to that after single intravenous administration of peramivir at the same doses in noninfected mice.

The AUC_{inf}, change in concentration over time, and trough concentration (plasma concentration at 24 hours post-dose) of plasma radioactivity and peramivir after repeated intravenous administration of 10 mg/kg ^{14}C-labeled peramivir QD for 14 days in male rats were almost comparable to those after single intravenous administration at the same dose. Although gender-related differences in the pharmacokinetics of peramivir have not been evaluated, toxicokinetic (TK) data have been generated in toxicity studies. As a result, there have been no marked gender-related differences in the TK parameters in any species, at any dose, or after single or repeated administration [see 3.(iii) Summary of toxicology studies].

3.(ii).A.(2) Distribution【4.2.2.3-01 - 04, 5.3.2.1-01】

Following a single intravenous dose of 24 mg/kg of ^{14}C-labeled peramivir in male rats, radioactivity levels peaked at 5 minutes post-dose in all tissues. Radioactivity declined to a level indistinguishable from background levels in the tissues excluding plasma, blood, kidney, liver, and lung at 8 hours post-dose and in all tissues at 48 hours post-dose. The radioactivity level in

[12] Area under the plasma concentration-time curve from time 0 to infinity
[13] Pharmacokinetics were non-linear at a single intravenous dose of 50 mg/kg of peramivir in mice.

the kidney at 5 minutes post-dose (165 μg eq./g) was about 2-fold the plasma radioactivity level (95.7 μg eq./g). The radioactivity levels in the lung and trachea were 31.5 and 15.1 μg eq./g, respectively, and the ratio of lung to plasma radioactivity concentration and the ratio of trachea to plasma radioactivity concentration were 0.33 and 0.16, respectively. Tissue radioactivity levels and their time courses after repeated intravenous administration of 24 mg/kg ^{14}C-labeled peramivir QD for 14 days in rats were similar to those after single intravenous administration and radioactivity in all tissues declined to a level indistinguishable from background levels at 72 hours after the last dose.

Following a single intravenous dose of 10 mg/kg of ^{14}C-labeled peramivir in pregnant rats (gestation day 19), radioactivity peaked at 5 minutes post-dose in most tissues and then disappeared rapidly from the tissues. Uterine radioactivity in pregnant rats also peaked at 5 minutes post-dose, but about half of the radioactivity level at 5 minutes post-dose was maintained at 15 minutes to 24 hours post-dose, which differed from the time courses in other tissues. Fetal and fetal tissue radioactivity levels were very low compared with maternal tissue levels, and radioactivity peaked at 1 hour post-dose in most tissues and then declined over time.

Following single intravenous doses of 10, 30, or 100 mg/kg of ^{14}C-labeled peramivir in juvenile (10 days of age) and adult (8 weeks of age) male rats, tissue radioactivity levels were linear over the dose range tested. Its distribution into the brain was very low in both juvenile and adult rats and the ratio of brain to plasma radioactivity concentration was ≤ 0.02.

In mice, rats, rabbits, monkeys, and humans, the *in vitro* serum protein binding and *in vitro* distribution in blood cells of ^{14}C-labeled peramivir were as low as 0.3% to 4.7% and 0% to 0.6%, respectively, over the concentration range tested (1-100 μg/mL).

3.(ii).A.(3) Metabolism【5.3.2.2-01, 4.2.2.4-01 - 03】

In an *in vitro* metabolism study of ^{14}C-labeled peramivir (100 and 300 μmol/L) using cryopreserved human hepatocytes, no metabolites were detected in the reaction solution. In an *in vivo* drug metabolism study, following a single intravenous dose of 10 mg/kg of ^{14}C-labeled peramivir in female mice, male rats, and female monkeys, only peramivir but no metabolites were detected in the samples from these animal species (plasma, urine, feces, bile).

3.(ii).A.(4) Excretion【4.2.2.5-01 - 05】

Following a single intravenous dose of 10 mg/kg of ^{14}C-labeled peramivir in male rats and female monkeys, the urinary excretion rate of radioactivity (the percent urinary excretion of the

administered radioactivity) was about 93% and about 94%, respectively, and the fecal excretion rate of radioactivity was about 6% and about 4%, respectively. Following a single intravenous dose of 10 mg/kg of ^{14}C-labeled peramivir in bile duct cannulated male rats, the urinary, biliary, and fecal excretion rates of radioactivity were about 96%, about 4%, and about 0.3%, respectively.

Following repeated intravenous administration of 10 mg/kg of ^{14}C-labeled peramivir QD for 14 days in male rats, the urinary and fecal excretion rates of radioactivity up to 168 hours after the last dose were about 92% and about 7%, respectively.

While coadministration of peramivir 10 mg/kg with probenecid 200 mg/kg in male rabbits resulted in a significant increase in plasma peramivir AUC_{inf} ($P < 0.01$, paired t-test) and a significant decrease in peramivir CL_{tot} ($P < 0.01$, paired t-test), there were no significant differences in any parameter in rats.

A single intravenous dose of 10 mg/kg of ^{14}C-labeled peramivir was administered to lactating rats (lactation days 11-13). The radioactivity level in milk (mean ± SD) at 0.5 hours post-dose was 0.698 ± 0.168 μg eq./mL, which was lower than the plasma radioactivity level (8.34 ± 0.68 μg eq./mL). The AUC_{inf} of radioactivity in milk was 8.99 ± 4.13 μg eq.·hr/mL, which was about half of the AUC_{inf} value of plasma radioactivity (17.1 ± 1.3 μg eq.·hr/mL). Radioactivity in milk declined over time and the radioactivity level in milk was decreased to about 1/20 of the C_{max} (0.919 ± 0.354 μg eq. /mL) at 24 hours post-dose.

3.(ii).A.(5) Pharmacokinetic drug interactions【4.2.2.6-01, 5.3.2.2-02 - 03】

In an *in vitro* CYP inhibition study, peramivir did not inhibit the major human liver cytochrome P450 isoforms (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) over the concentration range tested (0.01-100 μmol/L). In an *in vitro* CYP induction study, peramivir did not induce CYP1A2, CYP2A6, CYP2C9, CYP2D6, or CYP3A4 over the concentration range tested (0.05-10 μg/mL).

A study using an *in vitro* test system with Caco-2 cells revealed that peramivir is not a substrate for P-glycoprotein, nor it inhibits P-glycoprotein-mediated drug transport over the concentration range tested (3-300 μmol/L).

3.(ii).B *Outline of the review by PMDA*

3.(ii).B.(1) Drug concentration in the target organ/tissue

Taking into account that the drug concentration in the target organ/tissue was lower than the plasma concentration in a distribution study, PMDA asked the applicant to explain whether the therapeutic concentration of peramivir is maintained in the target organ/tissue for a necessary and sufficient period of time after a single intravenous dose of peramivir (clinical doses).

The applicant responded as follows:

Although a PK/PD study using a lethal murine model has demonstrated that the plasma pharmacokinetic parameter most correlated with the therapeutic effect of peramivir is AUC [see 3.(i) Summary of pharmacology studies], it is difficult to investigate the relationship between the upper airway fluid pharmacokinetics and efficacy in this study. It is also difficult to infer the relationship between the upper airway fluid AUC and efficacy in humans. On the other hand, it has been inferred that at both doses of 300 mg and 600 mg of peramivir, the drug concentration in the upper airway, i.e., the primary site of influenza virus infection (throat and nasal fluid concentrations) is maintained at a level exceeding the IC_{50} and IC_{90}[14] (22.2 ng/mL and 222 ng/mL, respectively) of a viral strain with the highest IC_{50} value among the clinical isolates from a phase III study (Study [redacted]15T0631) for a period of time equal to or longer than the time required for 1 cycle of viral replication (4-6 hours) (see the table below). Also given that peramivir is not readily dissociated from its bound the NA of influenza virus, peramivir at a therapeutic concentration should inhibit influenza virus replication in the upper airway and exert its efficacy.

Estimated peramivir concentrations in upper airway fluids following single intravenous doses of 300 mg and 600 mg of peramivir

Upper airway fluid concentration	Dose (mg)	Time from the start of infusion (15-minute infusion) (hr)							
		0.5	2	3*	4*	5*	6	12	24
Throat fluid concentration (ng/mL)	300	697	643	381	225	133	79	13	6
	600	1265	899	582	377	244	158	26	14
Nasal fluid concentration (ng/mL)	300	656	752	513	350	239	163	38	13
	600	1800	1860	1241	828	553	369	76	25

*: Estimated using the concentrations at 2 and 6 hours after the start of infusion, assuming that first-order elimination of the drug occurs from 2 hours until 6 hours after the start of infusion.

PMDA considers as follows:

Since peramivir is a NA inhibitor and does not have a mechanism of action of directly inhibiting viral replication, there are no solid grounds for claiming that the efficacy of peramivir is expected because a concentration exceeding the IC_{50} and IC_{90} values can be maintained for a

[14] Predicted from the IC_{50} value based on Banti et al.'s report (*Antimicrob Agent Chemother* 2001; 45: 1162-1167)

period of time equal to or longer than the time required for 1 cycle of viral replication (4-6 hours). However, given that peramivir is not readily dissociated from its bound NA in a non-clinical study [see 3.(i) Summary of pharmacology studies], although the drug concentration in the target organ/tissue is lower than the plasma concentration, the NA inhibitory activity of peramivir should be sustained for a certain period of time after peramivir administration.

3.(iii) Summary of toxicology studies

3.(iii).A *Summary of the submitted data*

Toxicity studies of peramivir conducted include single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, reproductive and developmental toxicity studies, and other toxicity studies (juvenile animal toxicity studies, an antigenicity study, nephrotoxicity studies). Doses are expressed in terms of peramivir.

3.(iii).A.(1) Single-dose toxicity【4.2.3.1-01 - 03】

Single-dose toxicity was evaluated in rat and monkey (2 divided doses/day) intravenous infusion studies and a monkey 24-hour continuous intravenous infusion study. The approximate lethal dose for both males and females was determined to be > 400 mg/kg (200 mg/kg × 2) in rats and > 120 mg/kg (60 mg/kg × 2) and > 720 mg/kg (24-hour continuous infusion) in monkeys. No toxicity findings were observed in any of the studies.

3.(iii).A.(2) Repeat-dose toxicity

Repeat-dose toxicity was evaluated in intravenous studies (1 month) and 24-hour continuous intravenous infusion studies (1 month) in rats and monkeys. There were no peramivir-related changes of toxicological significance in any of the studies. The margin of safety calculated by comparing the $AUC_{0\text{-}24hr}$ at the no observed adverse effect level (NOAEL) of peramivir from the 24-hour continuous intravenous infusion study in rats or monkeys (rats, 1440 mg/kg/day; monkeys, 720 mg/kg/day) with the predicted AUC_{τ}[15] at the maximum recommended human dose of peramivir (repeated intravenous administration of 600 mg QD) in Japanese healthy adult male subjects [see 4.(ii) Summary of clinical pharmacology studies] is about 18.9-fold and about 31.5-fold, respectively. The margin of safety between the NOAEL from the intravenous study in rats or monkeys (rats, 120 mg/kg/day; monkeys, 90 mg/kg/day) and the maximum recommended human dose is 9.2-fold and 7.3-fold, respectively, based on the C_{max} values. Although separate rabbit studies indicated that the target organ of toxicity is the kidney, it has been discussed that it is a species-specific toxicity related to the route of renal excretion of

[15] Area under plasma concentration-time curve during the dosing interval

peramivir [see 3.(iii).A.(7) Other toxicity studies and 3.(iii).B *Outline of the review by PMDA*].

3.(iii).A.(2).1) Rat studies

(a) One-month intravenous study【4.2.3.2-01】

Peramivir at doses of 0 (saline), 15, 40, and 120 mg/kg/day was intravenously administered (about 300 mL/kg/hour) for 28 days to rats. There were no peramivir-related changes and the NOAEL in this study was determined to be 120 mg/kg/day.

(b) One-month continuous intravenous infusion study【4.2.3.2-02】

Peramivir at doses of 0 (saline), 160, 480, and 1440 mg/kg/day was administered as a 24-hour continuous intravenous infusion (5 mL/kg/hour) for 30 days to rats. There were no peramivir-related changes and the NOAEL in this study was determined to be 1440 mg/kg/day.

3.(iii).A.(2).2) Monkey studies

(a) One-month intravenous study【4.2.3.2-03】

Peramivir at doses of 0 (saline), 10, 30, and 90 mg/kg/day was intravenously administered (about 45 mL/kg/hour) for 28 days to cynomolgus monkeys. There were no peramivir-related changes and the NOAEL in this study was determined to be 90 mg/kg/day.

(b) One-month continuous intravenous infusion study【4.2.3.2-04】

Peramivir at doses of 0 (saline), 120, 360, and 720 mg/kg/day was administered as a 24-hour continuous intravenous infusion (2.5 mL/kg/hour) for 30 days to cynomolgus monkeys. Although the kidney weight increased at ≥ 360 mg/kg, because the degree of change was slight and there were no associated clinical chemistry or histopathological changes, this finding was considered of little toxicological significance. After a 30-day recovery period, no increase in kidney weight was observed at 720 mg/kg. The NOAEL in this study was determined to be 720 mg/kg/day.

3.(iii).A.(3) Genotoxicity【4.2.3.3-01 - 03】

As genotoxicity studies, a bacterial reverse mutation test and an intravenous mouse bone marrow micronucleus test were performed, both of which produced negative results. In a chromosomal aberration assay using cultured mammalian cells (Chinese hamster ovary [CHO-K1] cells), after long continuous treatment without S9 mix, there was an increase in the frequencies of cells with numerical aberrations, which fell within historical negative control range. Thus, this finding was considered of no biological relevance. Based on the above study results, peramivir is considered to have no genotoxic potential.

3.(iii).A.(4) Carcinogenicity

No carcinogenicity studies have been conducted with peramivir because its expected clinical use is for a short period of time, genotoxicity studies produced negative results, and there was no accumulation or persistence of peramivir in any specific tissue [see 3.(ii).A.(2) Distribution]. Based on these results, peramivir is considered unlikely to have carcinogenic potential.

3.(iii).A.(5) Reproductive and developmental toxicity

As reproductive and developmental toxicity studies, studies of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a rat study on pre- and postnatal development, including maternal function were conducted. Although the embryo-fetal development studies showed effects on the urinary system (reduced renal papilla and dilated ureter) in rats (continuous infusion) and the occurrence of abortions and premature birth in rabbits, there were no other peramivir-related effects on the reproductive function of parent animals or embryo-fetal development, or neonatal growth and development. Placental transfer and milk excretion of peramivir in rats [see 3.(ii).A.(2) Distribution and 3.(ii).A.(4) Excretion] have been observed.

3.(iii).A.(5).1) Fertility and early embryonic development to implantation

(a) Male rat study【4.2.3.5-01】

Male rats were intravenously administered peramivir at doses of 0 (saline), 50, 200, 400, or 600 mg/kg/day (37-53 mL/kg/hour) from 10 weeks prior to and throughout mating with untreated females, and until the previous day of necropsy (about 13 weeks). Increased epididymis weight was observed at ≥ 400 mg/kg, which was within the laboratory background range and was not dose-related. Thus, this finding was considered unrelated to peramivir. Histopathologic examination of male reproductive organs including epididymis revealed no peramivir-related effects. The NOAELs in this study for male general toxicity and fertility and early embryonic development were all determined to be 600 mg/kg/day.

(b) Female rat study【4.2.3.5-02】

Female rats were intravenously administered peramivir at doses of 0 (saline), 50, 200, 400, or 600 mg/kg/day (66-76 mL/kg/hour) from 15 days prior and throughout mating with untreated males, and until gestation day 7 (about 25 days). Reductions in food consumption were observed prior to mating at ≥ 400 mg/kg and during gestation at 600 mg/kg, which were sporadic and minimal. Thus, these changes were considered of little toxicological significance. There were no peramivir-related effects on fertility or early embryonic development. The NOAELs in this study for female general toxicity and fertility and early embryonic development

were all determined to be 600 mg/kg/day.

3.(iii).A.(5).2) Embryo-fetal development

(a) Rat study【4.2.3.5-03】

Pregnant rats were intravenously administered peramivir at doses of 0 (saline), 200, 400, or 600 mg/kg/day (62-77 mL/kg/hour) from gestation day 6 to gestation day 17. There were no peramivir-related effects and the NOAEL in this study for maternal general and reproductive toxicity and embryo-fetal development were all determined to be 600 mg/kg/day.

(b) Rat study (continuous infusion)【4.2.3.5-04】

Pregnant rats received 0 (saline), 50, 400, or 1000 mg/kg/day of peramivir as a 24-hour continuous intravenous infusion (3.5 mL/kg/hour) from gestation day 6 to gestation day 17. Body weight gain increased during the dosing period at ≥ 50 mg/kg, which were minimal changes and there were no differences in body weight value at the end of the dosing period. Therefore, these changes were considered of no toxicological significance. While there were no peramivir-related effects on maternal reproductive function, fetal visceral examination revealed dose-dependent increases in the incidences of reduced renal papilla and dilated ureter at ≥ 50 mg/kg. The NOAELs in this study were determined to be 1000 mg/kg/day for maternal general and reproductive toxicity and < 50 mg/kg/day for embryo-fetal development.

(c) Rabbit study【4.2.3.5-05】

Pregnant rabbits were intravenously administered peramivir at doses of 0 (saline), 25, 50, 100, or 200 mg/kg/day (30-32 mL/kg/hour) from gestation day 7 to gestation day 19. Deaths at 100 and 200 mg/kg (1 of 22 animals, gestation day 9; 2 of 20 animals, gestation day 7 and gestation day 27), reductions in body weight gain and food consumption at ≥ 100 mg/kg, and abnormal stools (decreased stool output/no-feces, dry stool/loose stool/watery stool), emaciation, and whitish discolored cortex at 200 mg/kg were observed. As to effects on maternal reproductive function, abortions (2 of 22 animals, gestation day 23 and gestation day 25) and premature birth (1 of 22 animals, gestation day 29) occurred at 100 mg/kg and abortions (2 of 20 animals, gestation day 25 and gestation day 27) occurred at 200 mg/kg. Among the deaths, one animal receiving 100 mg/kg (gestation day 9) and one animal receiving 200 mg/kg (gestation day 7) exhibited no changes in clinical observations, body weight, or food consumption and their causes of death were unknown. The NOAELs in this study were determined to be 50 mg/kg/day for maternal general and reproductive toxicity and 200 mg/kg/day for embryo-fetal development.

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function【4.2.3.5-06】

Pregnant rats were intravenously administered peramivir at doses of 0 (saline), 50, 200, 400, or 600 mg/kg/day (52-70 mL/kg/hour) from gestation day 6 to lactation day 20. Low maternal body weights during lactation (lactation day 8) were noted at 600 mg/kg, which were transient, minimal changes and were not observed on other dosing days. Thus, this finding was considered of little toxicological significance. There were no peramivir-related effects on parturition or lactation. There were no peramivir-related effects on the physical/functional development or reproductive function of offspring. The NOAELs in this study for maternal general and reproductive toxicity and offspring developmental and reproductive toxicity were all determined to be 600 mg/kg/day.

3.(iii).A.(6) Local tolerance

No separate local tolerance study has been conducted. When the observations of the injection sites were performed in studies in rats, rabbits, and monkeys intravenously administered peramivir, there were no changes indicative of specific irritation. Thus, peramivir is considered to have little local irritant effect.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Juvenile animal toxicity studies

With a view to the use of peramivir in children, single and repeated intravenous studies in juvenile rats were conducted. There were no apparent differences in toxicities between juvenile and adult animals.

(a) Single intravenous study in juvenile rats【4.2.3.5-09】

Single intravenous doses of 0 (saline), 10, 120, and 240 mg/kg of peramivir (1794-5217 mL/kg/hour) were administered to juvenile rats (9 and 21 days of age). While no toxicity findings were observed in the animals at 9 days of age, animals at 21 days of age receiving 240 mg/kg exhibited transient irregular respiration and incomplete eyelid opening at 5 minutes post-dose. When plasma peramivir concentrations were compared between the age groups, there were no apparent differences in the C_0 while the $AUC_{0\text{-}24hr}$ was higher in the animals at 9 days of age. The approximate lethal dose was determined to be > 240 mg/kg (males and females) for both age groups.

(b) One-month intravenous study in juvenile rats【4.2.3.5-10】

Peramivir at doses of 0 (saline), 60, 120, and 240 mg/kg/day was intravenously administered

(722-5240 mL/kg/hour) for 28 days to juvenile rats (9 days of age). Low body weights in the latter half of the dosing period were noted at 240 mg/kg, which were slight in degree and the body weights recovered by the end of the dosing period. There were no abnormalities in the post-natal landmarks of development (coat growth, incisor eruption, open eyelid, righting reflex, cleavage of the balanopreputial gland, vaginal opening). When plasma peramivir concentrations were compared between Day 1 and Day 28, there were no apparent differences in the C_0 while the $AUC_{0\text{-}24hr}$ was higher on Day 1. The NOAEL in this study was determined to be 120 mg/kg/day.

3.(iii).A.(7).2) Antigenicity study in guinea pigs【4.2.3.7-01】

Guinea pig active systemic anaphylaxis (ASA) and passive cutaneous anaphylaxis (PCA) tests were performed. In a study where guinea pigs were sensitized with intravenous peramivir or subcutaneous peramivir plus adjuvant, the ASA and PCA reactions were both negative. Thus, peramivir is considered to have no antigenicity.

3.(iii).A.(7).3) Nephrotoxicity studies in rabbits

Since an embryo-fetal development study in rabbits [see 3.(iii).A.(5).2).(c) Rabbit study] and its dose-ranging study (Reference data, 4.2.3.5-08) showed changes suggestive of nephrotoxicity, single intravenous and 1-week intravenous studies were conducted to evaluate the nephrotoxicity of peramivir. Both studies revealed abnormalities in renal blood chemistry values, urinalysis and renal histopathological examination, indicating that the target organ of toxicity for peramivir is the kidney. The margin of safety between the NOAEL from the 1-week intravenous study and the maximum recommended human dose in Japanese healthy adult male subjects (repeated intravenous administration of 600 mg QD) [see 4.(ii) Summary of clinical pharmacology studies] is 2.4-fold based on the C_0 values and 2.3-fold based on the $AUC_{0\text{-}24hr}$ values. Tubular secretion via organic anion transporter (OAT) has been shown to contribute to the renal excretion of peramivir in rabbits [see 3.(ii).A.(4) Excretion], whereas it has been inferred that in humans and in rats that develop no nephrotoxicity even at higher exposures, peramivir is excreted by glomerular filtration and is not secreted by the renal tubules [see 3.(ii).A.(4) Excretion and 4.(ii) Summary of clinical pharmacology studies]. Therefore, it has been discussed that nephrotoxicity in rabbits is a species-specific toxicity related to the route of renal excretion of peramivir.

(a) Single intravenous study【4.2.3.7-02】

Single intravenous doses of 0 (saline), 50, 100, 200, and 300 mg/kg of peramivir (46-50 mL/kg/hour) were administered to rabbits. On the following day after dosing of peramivir at ≥

200 mg/kg, plasma urea nitrogen and creatinine were increased, urinalysis showed increased urine volume, urine protein, sugar in urine, increases in sodium and chloride, decreased potassium, and decreased specific gravity, and histopathological examination revealed increased kidney weight, renal hypertrophy, light brown discoloration of the renal cortex and medulla, dilatation and hyalin cast of the renal tubules, and tubular epithelial cell necrosis. No gender-related differences were noted and there were no renal effects at ≤ 100 mg/kg/day.

(b) One-week intravenous study【4.2.3.7-03】

Peramivir at doses of 0 (saline), 50, 100, and 200 mg/kg/day was intravenously administered (47-52 mL/kg/hour) for 7 days to rabbits (males). In 1 of 4 animals receiving 200 mg/kg, plasma urea nitrogen and creatinine were increased, urinalysis showed urine protein, sugar in urine, urinary occult blood, decreases in sodium and chloride, decreased potassium, and decreased specific gravity, and histopathological examination revealed light brown discoloration of the renal cortex, dilatation and hyalin cast of the renal tubules, and necrosis and regeneration of tubular epithelial cells. This animal also exhibited reduced body weight gain or reduced body weight, reduced food consumption, and decreased defecation. There were no renal effects at≤ 100 mg/kg/day.

3.(iii).B *Outline of the review by PMDA*

3.(iii).B.(1) Nephrotoxicity

PMDA asked the applicant to discuss the risk in humans pertaining to nephrotoxicity detected in rabbits.

The applicant responded as follows:

Nephrotoxicity was detected only in rabbits among the species used in toxicity studies (rats, monkeys, rabbits). Species differences in the renal excretion of peramivir were investigated. As a result, in rats, coadministration with probenecid, i.e., an organic anion transporter (OAT) inhibitor, did not alter the plasma peramivir concentration over time [see 3.(ii).A.(4) Excretion] and the route of renal excretion was considered to be glomerular filtration. In monkeys, although no coadministration study with probenecid has been conducted, since a single intravenous dose of peramivir was mostly excreted unchanged in urine (about 94%) [see 3.(ii).A.(3) Metabolism and 3.(ii).A.(4) Excretion], CL_{tot} was considered to approximate the renal clearance (CL_R) and furthermore, CL_{tot} [132-140 mL/hr/kg; see 3.(ii).A.(1) Absorption] almost agreed with the value obtained by dividing the glomerular filtration rate in monkeys (GFR, 10.4 mL/min, *Pharmaceutical Research* 1993; 10: 1093-1095) by body weight (5 kg) (124.8 mL/hr/kg). Thus, renal excretion was considered to occur by glomerular filtration in

monkeys. On the other hand, in rabbits, as coadministration with probenecid resulted in a significant increase in the AUC_{inf} and a significant decrease in the CL_{tot} of peramivir [see 3.(ii).A.(4) Excretion], tubular secretion was considered to contribute to renal excretion and it was inferred that tubular secretion may be involved in the development of nephrotoxicity detected in rabbits. In humans, coadministration with probenecid did not alter the plasma peramivir concentration over time [see 4.(ii) Summary of clinical pharmacology studies], and as with the cases of rats and monkeys, tubular secretion was not considered to contribute to renal excretion. Moreover, since there were no changes indicative of nephrotoxicity in clinical studies, nor were there any marked changes in renal parameters in a safety and pharmacokinetic study in patients with renal impairment, the risk of nephrotoxicity in humans should be low.

PMDA accepted the above response and considers as follows:
To date, there have been no direct experimental evidence to indicate that tubular secretion is associated with the nephrotoxicity of peramivir and the mechanism of nephrotoxicity has not been elucidated, but clinical studies have not suggested the risk of nephrotoxicity of peramivir [see 4.(iii).B.(2).3) Nephrotoxicity] and there is no particular concern about nephrotoxicity.

3.(iii).B.(2) Reproductive and developmental toxicity
PMDA asked the applicant to discuss the risk in humans pertaining to abortions and premature birth in rabbits and effects on the urinary system in rat fetuses (e.g., reduced renal papilla and dilated ureter) observed in reproductive and developmental toxicity studies.

The applicant responded as follows:
Since abortions and premature birth in pregnant rabbits were likely to be secondary to the deteriorated conditions of maternal animals and reduced food consumption induces abortion in rabbits (*Toxicology* 1981; 22: 255-259), the risk of similar events in humans should be low. However, these findings will be listed as the information obtained from laboratory animals in the package insert to call attention. On the other hand, effects on the urinary system observed in rat fetuses (e.g., reduced renal papilla and dilated ureter) are commonly reported findings as naturally occurring variations (*Cong Anom* 1997; 37: 47-138) and are considered transient delayed development of the urinary system and disappear after birth (*Teratology* 1972; 6: 191-196). Furthermore, other reproductive and developmental toxicity studies of peramivir showed no changes suggestive of the developmental retardation of the urinary system in fetuses or offsprings. Thus, these effects were considered of little toxicological significance. In addition, these findings were observed only with peramivir given as a 24-hour continuous intravenous infusion and there were no major differences in the predicted exposure ($AUC_{0\text{-}24hr}$) in maternal

animals between continuous infusion and non-continuous infusion in rat embryo-fetal development studies and the effects on the urinary system were inferred to be associated with a special dosing condition of long continuous exposure rather than the level of exposure. Therefore, the risk in humans at the proposed dosage regimen is low and there is no need to include a special caution statement in the package insert.

PMDA accepted the above response and considers as follows:
Although these reproductive and developmental toxicities observed in laboratory animals raise no particular concern for humans, peramivir has been shown to cross the placenta and it cannot be ruled out that these toxicities were associated with the direct effects of peramivir. Thus, peramivir should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks, and it is necessary to collect safety information on pregnant women/nursing mothers via post-marketing surveillance etc.

4. Clinical data

Peramivir Hydrate was used in clinical studies, but all concentrations and doses are expressed in terms of peramivir in this section.

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A *Summary of the submitted data*

No biopharmaceutic data have been submitted in this application. In clinical pharmacology studies, peramivir concentrations in human biomaterials (plasma, urine, throat gargles, nasal washes) were quantitated by LC/MS/MS.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A *Summary of the submitted data*

The results from the following pharmacokinetic studies of peramivir were submitted in this application: 2 phase I studies in Japanese healthy adult male subjects, 5 phase I studies in foreign healthy adult subjects,[16] 1 pharmacokinetic study in foreign healthy elderly subjects (foreign elderly study), 1 pharmacokinetic study in foreign subjects with renal impairment (foreign study in renal impairment subjects), 1 foreign phase II study in patients with influenza virus infection, 1 Japanese phase II study in patients with influenza virus infection, 1 Japanese phase III study in patients with influenza virus infection, and 1 multiregional phase III study in patients with influenza virus infection conducted in East Asian countries (Japan, Korea,

[16] The results from 3 studies (Study Hi-[redacted]-101, Study Hi-[redacted]-102, Study Hi-[redacted]-103) were submitted as reference data.

Taiwan).

4.(ii).A.(1) Japanese studies[17]

4.(ii).A.(1).1) Multiple-dose study in healthy adult male subjects【5.3.3.1-01, Study [redacted]12T0611 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of peramivir were evaluated in 24 Japanese healthy adult male subjects (the cases included in pharmacokinetic assessment). Subjects received the following treatments: (a) a single intravenous dose of 100 mg, 200 mg, or 400 mg of peramivir followed by an interval of 48 hours (no treatment on Day 2) and then the same dose of peramivir intravenously administered QD for 6 days from Day 3 onward or (b) a single intravenous dose of 400 mg of peramivir followed by an interval of 48 hours (no treatment on Day 2) and then the same dose of peramivir intravenously administered BID[18] for 6 days from Day 3 onward. Peramivir was infused over 15 minutes. The results were as shown in the following table. The pharmacokinetics of peramivir were linear over the dose range tested and there was little accumulation of peramivir after multiple-dose administration.

Pharmacokinetic parameters following multiple intravenous administration of peramivir 100 mg QD, 200 mg QD, and 400 mg QD or 400 mg BID

Dose	Pharmacokinetic assessment day	N	C_{max} (ng/mL)	AUC[b)] (ng·hr/mL)	$t_{1/2z}$ [c)] (hr)	Ur, total [d)] (%)	MRT [e)] (hr)
100 mg QD	Day 1	6	11200 ± 2900	17513 ± 2001	6.7 ± 4.6	91.47 ± 3.19	2.64 ± 0.33
	Day 8	6	10900 ± 2000	16436 ± 1540	23.6 ± 9.1		-
200 mg QD	Day 1	6	21100 ± 1600	33695 ± 3622	4.0 ± 0.2	77.17 ± 17.88	2.65 ± 0.27
	Day 8	6	19800 ± 2300	30358 ± 2980	28.4 ± 3.3		-
400 mg QD	Day 1	6	46800 ± 7000	63403 ± 8620	5.4 ± 3.8	92.60 ± 7.47	2.44 ± 0.28
	Day 8	6	45300 ± 8000	65409 ± 9498	29.3 ± 0.9		-
400 mg BID [a)]	Day 1	6	50500 ± 3800	68784 ± 6187	3.8 ± 0.1	80.22 ± 12.77	2.58 ± 0.23
	Day 8	6	45800 ± 5800	66182 ± 5169	30.1 ± 1.4		-

Mean ± SD
a) A single 400 mg dose on Days 1 and 8
b) AUC_{inf} (AUC from time 0 to ∞) for Day 1, AUC_{τ} (AUC from time 0 to the end of the dosing interval) for Day 8
c) Terminal phase elimination half-life
d) Cumulative urinary excretion up to the time of last measurement (% of the total dose)
e) Mean residence time

Summary statistics of the ratios of pharmacokinetic parameters (C_{max} and AUC) (throat and nasal fluids/plasma) after the first dose and the last dose were as shown in the following table.

[17] Including a phase III study (Study [redacted]15T0631) conducted in East Asian countries (Japan, Korea, Taiwan).
[18] On Day 8 (the last day of administration), a single intravenous 400 mg dose of peramivir was administered.

C_{max} and AUC ratios following multiple intravenous administration of peramivir 100 mg QD, 200 mg QD, and 400 mg QD or 400 mg BID (throat and nasal fluids/plasma)

Dose	Pharmacokinetic assessment day	N	Throat fluid		Nasal fluid	
			C_{max} ratio	AUC ratio[b)]	C_{max} ratio	AUC ratio[b)]
100 mg QD	Day 1	6	0.016 (76.0)	0.031 (33.8)	0.028 (47.2)	0.094 (31.3)
	Day 8	6	0.023 (44.0)	0.052 (40.9)	0.037 (73.3)	0.133 (60.8)
200 mg QD	Day 1	6	0.029 (61.2)	0.056 (47.4)	0.022 (56.6)	0.069 (47.1)
	Day 8	6	0.028 (39.9)	0.056 (33.9)	0.026 (35.1)	0.079 (34.2)
400 mg QD	Day 1	6	0.019 (38.3)	0.046 (23.3)	0.026 (28.8)	0.076 (22.9)
	Day 8	6	0.024 (37.8)	0.052 (37.2)	0.021 (62.7)	0.075 (39.9)
400 mg BID[a)]	Day 1	6	0.024 (58.1)	0.052 (39.6)	0.025 (58.3)	0.093 (30.9)
	Day 8	6	0.037 (46.2)	0.083 (27.7)	0.029 (148)	0.082 (85.7)

Geometric mean ratios (Geometric coefficient of variation [%])
a) A single 400 mg dose on Days 1 and 8
b) AUC_{inf} for Day 1, AUC_{τ} for Day 8

4.(ii).A.(1).2) High-dose study in healthy adult male subjects【5.3.3.1-02, Study [redacted]14T0612 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of peramivir following intravenous administration of peramivir 800 mg as a single dose or QD for 6 days (15-minute infusion) were evaluated in 12 Japanese healthy adult male subjects. The results were as shown in the following table. There was little accumulation of peramivir after multiple high-dose peramivir administration at 800 mg.

Pharmacokinetic parameters following intravenous administration of peramivir 800 mg as a single dose or QD for 6 days

Dose	Pharmacokinetic assessment day	N	C_{max} (ng/mL)	AUC[a)] (ng·hr/mL)	$t_{1/2z}$[b)] (hr)	Ur, total[c)] (%)	MRT[d)] (hr)
Single 800 mg dose	Day 1	6	86200 ± 15400	133795 ± 19972	23.7 ± 1.5	94.43 ± 2.30	2.83 ± 0.49
800 mg QD	Day 1	6	90400 ± 9200	136058 ± 13248	3.1 ± 0.2	85.09 ± 5.32	2.60 ± 0.18
	Day 6	6	85500 ± 13100	131385 ± 12871	28.6 ± 1.9		-

Mean ± SD
a) AUC_{inf} for Day 1 of single-dose and multiple-dose administration, AUC_{τ} for Day 6 of multiple-dose administration
b) Terminal phase elimination half-life
c) Cumulative urinary excretion up to the time of last measurement (% of the total dose)
d) Mean residence time

Summary statistics of the ratios of pharmacokinetic parameters (C_{max} and AUC) (throat and nasal fluids/plasma) after the first dose and the last dose were as shown in the following table.

C_{max} and AUC ratios following single and multiple (QD) intravenous administration of peramivir 800 mg (throat and nasal fluids/plasma)

Dose	Pharmacokinetic assessment day	N	Throat fluid		Nasal fluid	
			C_{max} ratio	AUC ratio[a)]	C_{max} ratio	AUC ratio[a)]
Single 800 mg dose	Day 1	6	0.019 (55.2)	0.038 (50.6)	0.034 (50.1)	0.088 (41.5)
800 mg QD	Day 1	6	0.029 (71.1)	0.067 (66.4)	0.023 (25.3)	0.065 (21.7)
	Day 6	6	0.024 (60.1)	0.061 (39.4)	0.019 (40.1)	0.074 (31.5)

Geometric mean ratios (Geometric coefficient of variation [%]) a) $AUC_{0\text{-}t}$ for Day 1, AUC_{τ} for Day 6

4.(ii).A.(1).3) Phase II single-dose study in patients with seasonal influenza virus infection 【5.3.5.1-01, Study [redacted]22T0621 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of single intravenous doses of peramivir 300 mg and 600 mg were evaluated in 198 Japanese patients with influenza virus infection. Peramivir was infused over 30 to 60 minutes and blood samples were collected immediately before the end of infusion and on Day 3 after the start of infusion (on Day 2 after the start of infusion, if possible) and plasma concentration data (558 sampling points) were obtained from 99 subjects in the peramivir 300 mg group and 99 subjects in the peramivir 600 mg group (101 males and 97 females in total). Using the plasma peramivir concentration data obtained from this study and the plasma concentration data (1092 sampling points) from 36 healthy adult male subjects in Japanese phase I studies (Studies [redacted]12T0611 and [redacted]14T0612), a population pharmacokinetic analysis (PPK analysis) was performed based on a 3-compartment model. As a result, creatinine clearance (CLcr) was found to affect CL and body weight (BWT) and gender[19] were found to affect the central compartment volume of distribution (V1). Differences in the pharmacokinetic parameters between healthy adults and patients with influenza virus infection were assessed after adjusting for CLcr, BWT, and gender. As a result, CL was 22% higher in patients compared with healthy adults and V1 differences at the mean body weights of male and female patients were 16% and 18%, respectively. The AUC values[20] (geometric mean) of peramivir at 300 mg and 600 mg in patients with influenza virus infection lay between the AUC values (geometric mean) at 200 mg and 400 mg and between the AUC values (geometric mean) at 400 mg and 800 mg in healthy adults, respectively, and the exposures in patients were within the range predicted from healthy adults.

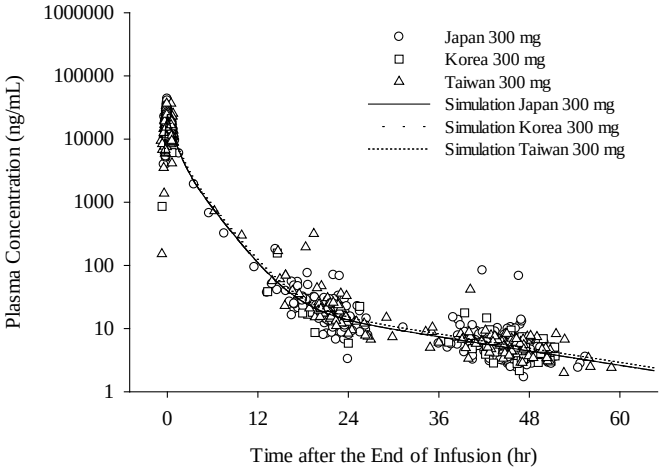
4.(ii).A.(1).4) Phase III single-dose study in patients with seasonal influenza virus infection 【5.3.5.1-02, Study [redacted]15T0631 ([redacted] 20[redacted] to [redacted] 20[redacted])】

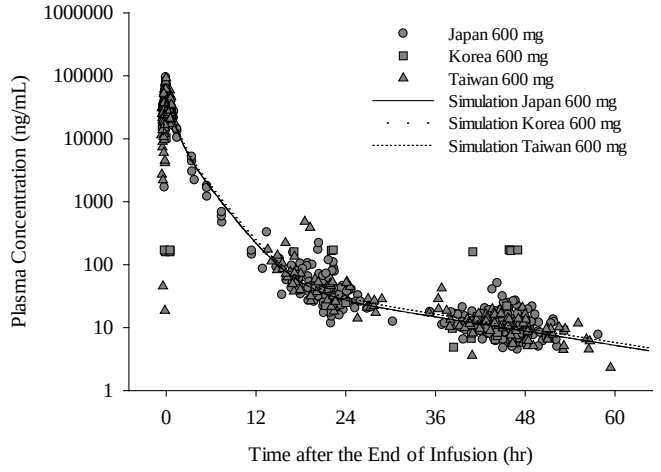
The pharmacokinetics of single intravenous doses of peramivir 300 mg and 600 mg were evaluated in 726 patients with influenza virus infection in Japan, Korea, and Taiwan. Peramivir was infused over 15 to 60 minutes and blood samples were collected immediately before the end of infusion and on Day 3 after the start of infusion (also on Day 2 after the start of infusion, where possible). PPK analysis was performed using the plasma concentration data (2115 sampling points) obtained from 364 subjects in the peramivir 300 mg group and 362 subjects in

[19] Since the healthy adult data from the Japanese phase I studies (Studies [redacted]12T0611[redacted] and [redacted]14T0612) did not include women, the applicant discussed that gender-related effects could not be assessed appropriately in this PPK analysis (PPK analysis of the Japanese phase I and phase II studies).

[20] Calculated from the individual Bayesian estimates of CL and the dose. Taking into account that 11.5% of the total dose of the investigational formulation was wasted in an infusion line (In-house material, Study Report (Report No: PMV-P(IV)1-AR1 R007). [redacted], 20[redacted]), the value that was 11.5% lower than the dose administered was used to calculate the pharmacokinetic parameter of plasma peramivir for this analysis.

the peramivir 600 mg group (379 males and 347 females in total). Using the plasma concentration data (a total of 3199 sampling points) from 332 subjects in Japanese phase I studies (Studies [redacted]12T0611 and [redacted]14T0612), a Japanese phase II study (Study [redacted]22T0621), a foreign phase I study (Study Hi-[redacted]-103), a foreign elderly study (Study Hi-[redacted]-104), and a foreign study in renal impairment subjects (Study Hi-[redacted]-105), pooled PPK analysis was performed based on a 3-compartment model. As a result, as CLcr and age were found to affect CL and BWT was found to affect V1, the analysis model included CLcr and age as sources of variation in CL and BWT as a source of variation in V1. Regional differences in the pharmacokinetic parameters were analyzed after adjusting for CLcr, age, and BWT, which revealed that CL and V1 in patients with influenza virus infection in Taiwan were both 8% lower than those in Japan and Korea while peramivir plasma concentrations over time (measured values) in patients with influenza virus infection and the population mean plasma concentration-time curve were similar among Japan, Korea, and Taiwan at both 300 mg and 600 mg (see the figures below).





Peramivir plasma concentrations (measured values) in patients with influenza virus infection and population mean plasma concentration over time in each region

Upper figure: 300 mg infusion, Lower figure: 600 mg infusion Plotted against time after the end of infusion
○: Japan, □: Korea, △: Taiwan
Solid line: Population mean plasma concentration over time for Japanese patients
Dashed line: Population mean plasma concentration over time for Korean patients
Dotted line: Population mean plasma concentration over time for Taiwanese patients

4.(ii).A.(1).5) Phase III single- and multiple-dose study in high-risk patients with seasonal influenza virus infection【5.3.5.2-01, Study [redacted]16T0632 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of single and multiple intravenous doses of peramivir 300 mg and 600 mg were evaluated in 42 Japanese high-risk patients (patients with poorly controlled diabetes, patients with chronic respiratory disease requiring pharmacotherapy, or patients currently on immunosuppressant medication) with influenza virus infection. Peramivir was infused over 15 to 60 minutes and blood samples were collected immediately before the end of infusion on Day

1, immediately before infusion on Day 2, and on the day after the last dose (also at any timepoint up to 12 hours after the first dose, where possible). The plasma concentration data (134 sampling points) were obtained from 21 subjects in the peramivir 300 mg group and 21 subjects in the peramivir 600 mg group (16 males, 26 females). The plasma concentration over time in this study was similar to those in Japanese phase I studies (Studies [redacted]12T0611 and [redacted]14T0612), a Japanese phase II study (Study [redacted]22T0621), and a multiregional phase III study (Study [redacted]15T0631) and there was no accumulation of peramivir after multiple-dose administration. Although there was no clear trend in the relationship between high-risk factors and plasma concentration, the plasma concentration during the elimination phase tended to be slightly higher in patients with impaired renal function (CLcr < 70 mL/min) compared with patients with normal renal function (CLcr ≥ 70 mL/min).

4.(ii).A.(2) Foreign studies

4.(ii).A.(2).1) Single-dose study in healthy adult subjects【5.3.3.1-03, Study Hi-[redacted]-101 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of a single intravenous dose of peramivir 0.5 mg/kg (15-minute infusion) were evaluated in 6 foreign healthy adult subjects (4 males, 2 females). The C_{max}, AUC_{inf}, and $t_{1/2}$ (mean ± SD) following a single intravenous dose of peramivir 0.5 mg/kg were 1925.8 ± 521.1 ng/mL, 4975.2 ± 593.4 ng·hr/mL, and 2.9 ± 0.53 hours, respectively, and the mean cumulative urinary excretion up to 48 hours post-dose (range) was 24.9 mg (1.6-69.3). The plasma concentration at 48 hours after a single intravenous dose of peramivir 0.5 mg/kg was below the lower limit of quantification (1 ng/mL) in all subjects.

4.(ii).A.(2).2) Multiple-dose study in healthy adult subjects【5.3.3.1-04, Study Hi-[redacted]-102 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of peramivir 0.5 mg/kg intravenously administered BID for 1 day (30-minute infusion) were evaluated in 6 foreign healthy adult subjects (5 males, 1 female). As a result, the C_{max}, AUC_{τ}, and $t_{1/2}$ after the first and second infusions (mean ± SD) in subjects intravenously administered peramivir 0.5 mg/kg BID for 1 day were 2589.2 ± 381.5 and 2549.2 ± 362.3 ng/mL, 5954.7 ± 699.2 ng·hr/mL and 6035.9 ± 800.8 ng·hr/mL, and 2.1 ± 0.2 hours and 2.2 ± 0.193 hours, respectively, and the mean cumulative urinary excretion up to 48 hours post-dose (range) was 72.3 mg (44.0-125.4).

4.(ii).A.(2).3) Single- and multiple-dose study in healthy adult subjects【5.3.3.1-05, Study Hi-[redacted]-103 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of peramivir were evaluated in 49 foreign healthy adult subjects (33

males, 16 females). Peramivir was infused over 15 minutes and the assigned treatments were: (a) single intravenous doses of peramivir 1, 2, 4, and 8 mg/kg (Cohort 1, 2, 3, and 4, respectively; 6 subjects per cohort), (b) intravenous administration of peramivir 4 mg/kg BID for 1 day (Cohort 5, 7 subjects), and (c) intravenous administration of peramivir 2 and 4 mg/kg BID for 10 days (Cohort 6, 9 subjects per dose). As a result, the pharmacokinetic parameters of peramivir (C_{max} and AUC) were linear over the dose range of 1 to 8 mg/kg and there was no accumulation of peramivir after multiple-dose administration of peramivir 2 or 4 mg/kg BID for 10 days.

4.(ii).A.(2).4) Pharmacokinetic study in subjects with renal impairment【5.3.3.3-01, Study Hi-[redacted]-105 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of peramivir given as an intravenous infusion were evaluated in 6 foreign subjects with normal renal function (4 males, 2 females) and 24 subjects with renal impairment (11 males, 13 females). The degree of renal impairment was classified into Cohort 1 "normal (CLcr > 80 mL/min)," Cohort 2 "mild (CLcr 50-80 mL/min)," Cohort 3 "moderate (CLcr 30-49 mL/min)," and Cohort 4 "severe (CLcr < 30 mL/min)." These cohorts of subjects received peramivir 2 mg/kg as a single intravenous infusion over 15 minutes (6 subjects per cohort). Subjects with end-stage renal disease (N = 6) were assigned to Cohort 5 and intravenously administered peramivir 2 mg/kg at 2 hours prior to the start of dialysis on Day 1 and after the completion of dialysis on Day 12. The results were as shown in the following table. It was demonstrated that elimination of peramivir from the body is delayed and the exposure (AUC) is increased in subjects with renal impairment.

Pharmacokinetic parameters following a single intravenous dose of peramivir 2 mg/kg (15-minute infusion) in subjects with varying degrees of renal function

	Cohort 1 (normal)	Cohort 2 (mild renal impairment*)	Cohort 3 (moderate renal impairment)	Cohort 4 (severe renal impairment*)
C_{max} (ng/mL)	12800 ± 2860	12500 ± 3590	13700 ± 3780	13200 ± 2910
T_{max} a) (hr)	0.25 (0.25-0.30)	0.25 (0.23-1.00)	0.25 (0.23-0.32)	0.25 (0.23-0.28)
$AUC_{0\text{-}t}$ (ng·hr/mL)	26000 ± 3200	33900 ± 7870	108000 ± 31200	136000 ± 40600
AUC_{inf} (ng·hr/mL)	26000 ± 3180	33900 ± 7880	108000 ± 31200	137000 ± 41100
$t_{1/2,z}$ (hr)	20.7 ± 4.78	23.7 ± 2.84	28.7 ± 3.21	30.7 ± 2.75
CL (mL/min)	108 ± 9.90	77.9 ± 21.4	26.8 ± 5.35	21.1 ± 4.68
Vss (L)	22.0 ± 4.35	20.6 ± 6.07	21.9 ± 3.40	23.5 ± 2.80
CL_R (mL/min)	97.1 ± 9.23	66.3 ± 15.8	23.2 ± 5.59	14.7 ± 3.27
Ur b) (%)	90.4 ± 7.5	86.0 ± 8.5	85.9 ± 5.5	71.6 ± 16.4 [21]

Mean ± SD
No. of subjects evaluated: N = 6
(*: One subject with mild renal impairment and 1 subject with severe renal impairment were excluded as the infusion time was ≥ 15 minutes due to a malfunctioning of the pump.)
a) Median (range)
b) Cumulative urinary excretion rate up to 168 hours post-dose
Mean body weight: 83.7 kg (normal), 71.9 kg (mild), 83.7 kg (moderate), 77.7 kg (severe)

[21] The applicant discussed that the cumulative urinary excretion rate may be underestimated due to an inadequate duration of urine sampling in subjects with severe renal impairment.

Pharmacokinetic parameters following a single intravenous dose of peramivir 2 mg/kg (15-minute infusion) in subjects with end-stage renal disease

	End-stage renal disease (ESRD)	
	Pre-dialysis	After dialysis
C_{max} (ng/mL)	11000 ± 3000	15500 ± 3610
T_{max} [a)] (hr)	0.25 (0.25-2.25)	0.25 (0.25-1.25)
AUC_{0-t} (ng·hr/mL)	107000 ± 20300 [b)]	470000 ± 81200 [c)]
$t_{1/2,z}$ (hr)	70.6 ± 33.9 [b)]	93.1 ± 53.3 [c)]

Mean ± SD; No. of subjects evaluated: N = 6
a) Median (range)
b) Calculated using data up to 48 hours after the end of infusion
c) Calculated using data up to 72 hours after the end of infusion

The percentage of peramivir removed by dialysis [(arterial concentration − venous concentration)/arterial concentration × 100 (%)] in the ESRD group ranged from 73.3% to 81.3%.

4.(ii).A.(2).5) Pharmacokinetic study in healthy elderly subjects【5.3.3.3-02, Study Hi-[redacted]-104 ([redacted] 20[redacted] to [redacted] 20[redacted])】

The pharmacokinetics of peramivir 4 mg/kg intravenously administered BID for 1, 5, and 10 days (15-minute infusion) were evaluated in 20 foreign healthy elderly subjects (10 males, 10 females, 65-79 years of age). In Part I (Day 1), 20 subjects were intravenously administered peramivir 4 mg/kg BID for 1 day and in Part II (from Day 3), 12 of the 20 subjects from Part I (6 subjects treated with peramivir per group) were intravenously administered peramivir 4 mg/kg BID for 5 days (Group A) or 10 days (Group B). The results were as shown in the following table.

Pharmacokinetic parameters following multiple intravenous doses of peramivir (15-minute infusion) in elderly subjects

	4 mg/kg BID		
	Part I (for 1 day, the first dose)	Part II, Group A (for 5 days, the last dose)	Part II, Group B (for 10 days, the last dose)
C_{max} (ng/mL)	22647.5 ± 4823.7	22608.3 ± 4910.7	22933.3 ± 2951.2
AUC_{0-12hr} (ng·hr/mL)	61334.0 ± 8793.4	70465.4 ± 12236.4	61572.3 ± 8564.4
CL (mL/hr/kg)	-	58.2 ± 10.2	66.3 ± 11.5
CL (mL/min)	-	79.5 ± 13.1	77.7 ± 15.4
Vss (mL/kg)	-	267.7 ± 28.6	270.2 ± 31.7

Mean ± SD -: Not calculated
No. of subjects evaluated Part I: N = 20, Part II: N = 6 per group
Mean body weight, 78.3 kg

4.(ii).A.(2).6) Dose-escalating, three-period crossover study in healthy adult subjects (drug interaction study of peramivir with probenecid)【5.3.3.4-01, Study Him-[redacted]-111 ([redacted] 20[redacted] to [redacted] 20[redacted])】

A three-treatment, three-period crossover study was conducted in 27 foreign healthy adult subjects (23 males, 4 females) to evaluate the pharmacokinetics of peramivir 75 mg, 150 mg,

and 300 mg administered as a single intravenous dose (Treatment A, 15-minute infusion), as a single intramuscular dose (Treatment B), and as a single intramuscular dose in combination with probenecid 1 g (Treatment C). The results were as shown in the following table. The route of administration did not affect bioavailability (BA) and coadministration with probenecid did not alter the pharmacokinetics of peramivir. CL_R was within the normal range of glomerular filtration rate for healthy adults and CL_R was almost equal to glomerular filtration rate. Thus, it was discussed that the renal excretion of peramivir occurs largely through glomerular filtration with little involvement of tubular secretion or reabsorption.

Pharmacokinetic parameters of peramivir administered as a single intravenous dose, as a single intramuscular dose, and as a single intramuscular dose in combination with probenecid

Parameter	Dose (mg)	Treatment A (Single intravenous dose)	Treatment B (Single intramuscular dose)	Treatment C (Single intramuscular dose in combination with probenecid)
		N = 9	N = 9	N = 8
C_{max} a) (ng/mL)	75	5740 ± 817 e)	4300 ± 760	4550 ± 975
	150	11100 ± 2680	7610 ± 884 e)	7530 ± 1420
	300	20400 ± 1730	15200 ± 2370	15600 ± 2210
T_{max} b) (hr)	75	0.25 (0.25-0.27) e)	0.50 (0.50-0.50)	0.50 (0.50-1.00)
	150	0.25 (0.23-0.28)	0.56 (0.50-1.00) e)	0.50 (0.50-0.50)
	300	0.25 (0.23-0.28)	0.50 (0.50-0.50)	0.50 (0.50-1.00)
AUC_{0-t} (ng·hr/mL)	75	11000 ± 1650 e)	10800 ± 1190	11000 ± 1350
	150	24600 ± 4000	22700 ± 3600 e)	21400 ± 2480
	300	47900 ± 5100	47200 ± 5370	50000 ± 6310
AUC_{inf} (ng·hr/mL)	75	11000 ± 1750 f)	10800 ± 1170	11000 ± 1380 f)
	150	24700 ± 4010	22800 ± 3610 e)	21500 ± 2460
	300	48000 ± 5130	47300 ± 5390	50100 ± 6370
$t_{1/2,\ z}$ (hr)	75	13.8 ± 2.52 f)	25.2 ± 19.9	16.5 ± 5.45 f)
	150	26.0 ± 6.33	24.8 ± 3.07 e)	25.2 ± 3.32
	300	21.7 ± 2.12	22.8 ± 2.45	21.5 ± 1.98
CL c) (mL/min)	75	116 ± 18.1 f)	117 ± 12.5	115 ± 14.5 f)
	150	104 ± 15.6	112 ± 17.2 e)	118 ± 11.9
	300	105 ± 11.3	107 ± 11.3	101 ± 12.3
Vd d) (L)	75	20.0 ± 2.59 f)	265 ± 247	160 ± 36.1 f)
	150	20.2 ± 3.78	242 ± 53.6 e)	257 ± 45.8
	300	22.4 ± 2.21	211 ± 36.6	187 ± 11.7
CL_R (mL/min)	75	105 ± 20.6 g)	111 ± 14.1 e)	107 ± 13.9 f)
	150	98.4 ± 29.6 e)	101 ± 13.1 e)	105 ± 10.4
	300	94.9 ± 23.5 f)	96.5 ± 12.0	93.7 ± 12.4 g)
Ur (%)	75	89.5 ± 5.7 f)	94.9 ± 6.8 e)	91.4 ± 6.6
	150	94.1 ± 18.8 e)	90.7 ± 6.1 e)	89.7 ± 8.0
	300	91.4 ± 17.3 f)	90.4 ± 7.2	94.5 ± 2.9 g)
BA (%)	75	-	98.6	-
	150	-	92.3	-
	300	-	98.5	-

a) The concentration at the end of infusion was extrapolated from measured data in the intravenous dose group.
b) Median (range) c) Treatment B and C groups: CL/F
d) Treatment A group: Vss, Treatment B and C groups: Vz/F
e) N = 8 f) N = 7 g) N = 6 -: Not calculated

4.(ii).A.(2).7) Thorough QT/QTc study in healthy adult subjects【5.3.4.1-01, Study BCX1812-106 ([redacted] to [redacted])】

A four-treatment, four-period crossover study was conducted in 52 foreign healthy adult subjects (26 males, 26 females) to assess the correlation between the pharmacokinetics of

peramivir and QT interval prolongation (13 subjects per sequence). Subjects received each of the following treatments: a single intravenous dose of peramivir 600 mg (Treatment A, 30-minute infusion), a single intravenous dose of peramivir 1200 mg (Treatment B, 30-minute infusion), placebo (Treatment C), and a single oral dose of moxifloxacin (MFLX) 400 mg as a positive control (Treatment D). As pharmacokinetic data, the plasma concentration data at 13 sampling points during the period from 40 to 1415 minutes after the start of administration of peramivir and MFLX (only 5 sampling points during the period from 95 to 755 minutes after the start of administration of MFLX) were used. As a result, a single intravenous dose of peramivir 600 mg or 1200 mg had no effects on QT/QTc interval (no gender-related differences), nor was there any correlation between an increase in plasma peramivir concentration and QTcF interval prolongation.

Pharmacokinetic parameters following single intravenous doses of peramivir 600 mg and 1200 mg (30-minute infusion)

	Treatment A (Peramivir 600 mg)	Treatment B (Peramivir 1200 mg)
C_{max} [a)] (ng/mL)	43804.08 ± 7561.08	93206.12 ± 14729.62
T_{max} [b)] (hr)	0.67 (0.67) [c)]	0.67 (0.67-0.83)
AUC_{0-t} (ng·hr/mL)	96654.57 ± 17435.72	199162.11 ± 34532.96
AUC_{inf} (ng·hr/mL)	96950.21 ± 17498.60	199719.30 ± 34670.56

Arithmetic mean ± SD No. of subjects evaluated N = 49
a) Plasma peramivir concentration at 40 minutes after the start of infusion
b) Median (Min-Max)
c) The minimum value was equal to the maximum value.

4.(ii).B *Outline of the review by PMDA*

4.(ii).B.(1) Exposure in low-body-weight patients

PMDA asked the applicant to explain the exposure of peramivir at 600 mg in low-body-weight patients (< 30 kg) (C_{max}, a pharmacokinetic parameter influenced by body weight).

The applicant responded as follows:

The simulation results for C_{max} in patients weighing 20 to 30 kg with varying degrees of renal function were as shown in the following table.

Effects of body weight on C_{max} in patients with varying degrees of renal function

	C_{max} (ng/mL)			
	Body weight 20-30 kg	Body weight 30-50 kg	Body weight 50-80 kg	Body weight 80-120 kg
Normal (CLcr 80-140 mL/min)	94914 (75383-115879)	71158 (54102-92671)	50288 (37607-67146)	35337 (26142-47423)
Mild renal impairment (CLcr 50-80 mL/min)	102952 (80861-129228)	75835 (56562-99462)	52237 (38782-70655)	36230 (26639-49203)
Moderate renal impairment (CLcr 30-50 mL/min)	108936 (85005-137848)	78845 (58000-105210)	53529 (39274-72774)	36891 (26837-50039)
Severe renal impairment (CLcr 10-30 mL/min)	114356 (87366-146053)	81325 (60178-109567)	54575 (39744-75234)	37275 (27184-51197)

Peramivir 600 mg administration (normalized to 531 mg) Median (90% prediction range)

The C_{max} [median (90% prediction interval)] following a single intravenous dose of peramivir

600 mg (15-minute infusion) in low-body-weight (20-30 kg) patients with mild renal impairment (CLcr = 50-80 mL/min) was 102952 ng/mL (80861-129228). On the other hand, the geometric mean C_{max} (Min-Max) following a single high-dose (800 mg) intravenous administration of peramivir in a Japanese phase I study (Study [redacted]14T0612) was 85200 ng/mL (72300-112000). Although it is inferred that the C_{max} is slightly higher in low-body-weight (20-30 kg) patients with mild renal impairment than in healthy adults, its difference is not very large (approximately 20%). In a foreign thorough QT/QTc study (Study BCX1812-106), when a single intravenous dose of peramivir 1200 mg was administered over 30 minutes, the plasma concentration at 40 minutes after the start of infusion (mean ± SD) was 93206 ± 14729 ng/mL. Thus, the plasma concentration immediately before the end of infusion (at 30 minutes after the start of infusion) is inferred to be even higher and the C_{max} of peramivir at 600 mg in low-body-weight (20-30 kg) patients with mild renal impairment is inferred to be within the C_{max} range following a single dose of 1200 mg (30-minute infusion) in healthy adults. Peramivir has been demonstrated to be tolerable and safe at an exposure level of > 800 mg (15-minute infusion) overseas, though it was studied up to 800 mg in Japan. Therefore, no dose adjustment is required for low-body-weight patients weighing 20 to 30 kg as well.

PMDA considers that the C_{max} (predicted value) following a single intravenous dose of peramivir 600 mg in low-body-weight (20-30 kg) patients with mild renal impairment is unlikely to substantially deviate from the C_{max} range following a single dose of peramivir 1200 mg (30-minute infusion) that has been demonstrated to be safe in healthy adults. Thus, PMDA accepted the applicant's response above which claims that no dose adjustment based on body weight is required. See "4.(iii).B.(4) Dosage and administration" for the proposed dosage and administration.

4.(ii).B.(2) Drug interactions

PMDA asked the applicant to explain the potential for drug-drug interactions when peramivir is coadministered with other renally excreted drugs, based on the results of *in vitro* and *in vivo* studies.

The applicant responded as follows:

A drug interaction study with probenecid in foreign healthy adult subjects (Study Him-[redacted]-111) suggested that coadministration with probenecid did not affect the pharmacokinetics of peramivir and peramivir does not undergo organic anion transporter (OAT1 and OAT3)-mediated tubular secretion. In an *in vitro* test system, it has been shown that peramivir is not a substrate for P-gp [see 3.(ii).A.(5) Pharmacokinetic drug interactions], and peramivir thus

is not likely to undergo P-gp-mediated tubular secretion. Therefore, it is inferred that peramivir undergoes little transporter-mediated active tubular secretion. The renal clearances of intramuscular peramivir, intramuscular peramivir in combination with probenecid, and intravenous peramivir were 97 to 111, 94 to 107, and 95 to 105 mL/min, respectively, which were within the normal range of glomerular filtration rate for healthy adults. The results have suggested that peramivir is renally excreted primarily by glomerular filtration with little tubular secretion or reabsorption. Based on the above findings, since peramivir is unlikely to be a substrate for OAT or P-gp, there is little possibility that peramivir may undergoe drug interaction with drugs affecting these transporters, or that peramivir may cause competitive interaction with other drugs via the transporters. Furthermore, peramivir is unlikely to interact with other drugs via glomerular filtration (passive diffusion). Accordingly, it has been concluded that even when peramivir is coadministered with other renally excreted drugs, there is little possibility that peramivir may undergoe drug interaction with the concomitant drug or cause drug interaction that affects the renal excretion of the concomitant drug.

PMDA accepted the applicant's explanation that based on the submitted study data, when peramivir is coadministered with other renally excreted drugs, pharmacokinetic drug interactions are unlikely to occur.

4.(ii).B.(3) Inter-individual variability in urinary excretion rate

PMDA asked the applicant to explain whether there are differences in the demographic factors and the occurrence of adverse events between subjects with a cumulative urinary excretion rate of ≥ 50%[22] and subjects with a cumulative urinary excretion rate of < 50%[23] in Japanese and foreign phase I studies.

The applicant responded as follows:

In Japanese phase I studies (Studies [redacted]12T0611 and [redacted]14T0612) and foreign phase I studies (Studies Hi-[redacted]-101, Hi-[redacted]-102, and Hi-[redacted]-103), there was an imbalance in the number of subjects between the subgroup with a urinary excretion rate of < 50% and the subgroup with a urinary excretion rate of ≥ 50%. Thus, appropriate comparison is not possible, but there were no major differences in the demographic factors (age, height, body weight, BMI, race, ethnic group[24]). There were also no apparent differences in the occurrence of adverse events (the incidence by SOC, PT, or severity) between the two subgroups.

[22] ≥ 50%: The urinary excretion rate by treatment day was ≥ 50% on all days.
[23] < 50%: The urinary excretion rate by treatment day was < 50% at least once.
[24] Racial and ethnic comparisons were made in the foreign phase I studies only (Studies Hi-[redacted]-101, Hi-[redacted]-102, and Hi-[redacted]-103).

PMDA considers as follows:

Because there was no trend towards major differences in the occurrence of adverse events (the incidence by SOC, PT, or severity) between the two subgroups, although the cause of inter-subject variability in cumulative urinary excretion rate has not been identified at present, the inter-individual variability in urinary excretion rate is unlikely to affect safety.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A *Summary of the submitted data*

As the evaluation data, the results from the following studies were submitted in this application: 2 Japanese phase I studies, 4 foreign phase I studies, 1 Japanese phase II study, 1 Japanese phase III study, and 1 multiregional phase III study. As the reference data, the results from 3 foreign phase I studies and 1 foreign phase II study were submitted.

List of clinical studies

Evaluation data						
Geographical location	Phase	Study Number	Study population	No. of treated subjects	Dosage regimen[2)]	Treatment duration
Japan	I	[redacted]12T0611	Healthy adult male subjects	32	Step I: Peramivir 100, 200, 400 mg, or placebo QD Step II: Peramivir 400 mg or placebo BID	8 days (no treatment on Day 2)
Japan	I	[redacted]14T0612	Healthy adult male subjects	16	Step I: Peramivir 800 mg or placebo Step II: Peramivir 800 mg or placebo QD	Step I: Single dose Step II: 6 days
Overseas	I	Hi-[redacted]-105	Subjects with renal impairment and healthy adult subjects	30	Peramivir 2 mg/kg	Single dose
Overseas	I	Hi-[redacted]-104	Healthy elderly subjects (≥ 65 years of age)	20	Part I: Peramivir 4 mg/kg BID Part II: Peramivir 4 mg/kg or placebo BID	Part I: 1 day Part II: 5 or 10 days
Overseas	I	BCX1812-106	Healthy adult subjects	52	Treatment A: Peramivir 600 mg and MFLX placebo (oral) Treatment B: Peramivir 1200 mg and MFLX placebo (oral) Treatment C: Peramivir placebo and MFLX placebo (oral) Treatment D: MFLX 400 mg (oral) and Peramivir placebo	Single dose, 4-period
Overseas	I	Him-[redacted]-111	Healthy adult subjects	27	Treatment A: Peramivir 75, 150, or 300 mg Treatment B: Peramivir 75, 150, or 300 mg (intramuscular) Treatment C: Peramivir 75, 150, or 300 mg (intramuscular) + probenecid 1 g (oral)	Single dose, 3-period
Japan	II	[redacted]22T0621	Patients with influenza virus infection	298	Peramivir 300, 600 mg, or placebo	Single dose
East Asia[1)]	III	[redacted]15T0631	Patients with influenza virus infection	1093	Peramivir 300, 600 mg or oseltamivir phosphate 75 mg BID (oral)	Peramivir: Single dose Oseltamivir phosphate: 5 days
Japan	III	[redacted]16T0632	High-risk patients with influenza virus infection	42	Peramivir 300, 600 mg	Single or multiple doses (up to 5 days)

Evaluation data						
Geographical location	Phase	Study Number	Study population	No. of treated subjects	Dosage regimen[2)]	Treatment duration
Reference data						
Geographical location	Phase	Study Number	Study population	No. of treated subjects	Dosage regimen	Treatment duration
Overseas	I	Hi-[redacted]-101	Healthy adult subjects	8	Peramivir 0.5 mg/kg	Single dose
Overseas	I	Hi-[redacted]-102	Healthy adult subjects	8	Peramivir 0.5 mg/kg BID	1 day
Overseas	I	Hi-[redacted]-103	Healthy adult subjects	68	Part I: Peramivir 1, 2, 4, 8 mg/kg (Cohorts 1-4) or placebo Part II: Cohort 5, placebo or Peramivir 4 mg/kg BID; Cohort 6, placebo, Peramivir 2 or 4 mg/kg BID	Part I: Single dose Part II: Cohort 5, 1 day; Cohort 6, 10 days
Overseas	II	BCX1812-201	Patients with severe or potentially life-threatening influenza virus infection	137	Peramivir 200, 400 mg, or oseltamivir phosphate 75 mg BID (oral)	5 days

QD: once daily BID: twice daily

1) Conducted as a multiregional clinical study in a total of 3 countries (Japan, Korea, Taiwan).

2) Unless otherwise specified, the study drug was administered as a single intravenous dose.

Among the above submitted data, the main clinical studies are summarized below.

4.(iii).A.(1) Clinical pharmacology studies

4.(iii).A.(1).1) Multiple-dose study in Japanese healthy adult male subjects【5.3.3.1-01, Study [redacted]12T0611 ([redacted] 20[redacted] to [redacted] 20[redacted])】

A randomized, double-blind, placebo-controlled study was conducted at a single center in Japan to evaluate the tolerability, safety, and pharmacokinetics of peramivir in Japanese healthy adult male subjects [Target sample size of 32 (Step I [Step I -1-3], 18 subjects in the peramivir groups [6 subjects each in the peramivir 100, 200, and 400 mg groups] and 6 subjects in the placebo group [2 subjects per group]; Step II, 6 subjects in the peramivir 400 mg group and 2 subjects in the placebo group)].

In Step I, peramivir 100 mg or placebo (Step I-1), peramivir 200 mg or placebo (Step I-2), and peramivir 400 mg or placebo (Step I-3) were to be intravenously administered QD for 8 days (no treatment on Day 2). After safety in Step I was confirmed, in Step II, peramivir 400 mg or placebo was to be intravenously administered BID for 8 days (QD on Days 1 and 8, no treatment on Day 2).

Of the 44 subjects enrolled into the study, a total of 32 subjects, excluding 3 reserve subjects[25] in each group, were included in the safety analysis population.

In Step I, adverse events occurred in 3 subjects treated with peramivir (3 events) (nausea in the peramivir 100 mg group, urticaria and toothache in the peramivir 400 mg group) and 1 subject treated with placebo (2 events) (oral discomfort and diarrhoea). In Step II, no adverse events were reported in either treatment group. Of these adverse events, those for which a causal relationship to the study drug could not be denied (hereinafter referred to as adverse drug reactions) were nausea reported by 1 subject in the peramivir 100 mg group and diarrhoea and oral discomfort reported by 1 subject in the placebo group in Step I.

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(iii).A.(1).2) High-dose study in Japanese healthy adult male subjects【5.3.3.1-02, Study [redacted]14T0612 ([redacted] 20[redacted] to[redacted] 20[redacted])】

A randomized, double-blind, placebo-controlled study was conducted at a single center in Japan to evaluate the tolerability, safety, and pharmacokinetics of peramivir in Japanese healthy adult male subjects [Target sample size of 16 (Step I, 6 subjects in the peramivir 800 mg group and 2 subjects in the placebo group; Step II, 6 subjects in the peramivir 800 mg group and 2 subjects in the placebo group)].

In Step I, a single intravenous dose of peramivir 800 mg or placebo was to be administered. After safety in Step I was confirmed, in Step II, peramivir 800 mg or placebo was to be intravenously administered QD for 6 days.

Of the 22 subjects enrolled into the study, a total of 16 subjects (subjects treated with the study drug), excluding 3 reserve subjects[26] in each Step, were included in the safety analysis population.

No adverse events or adverse drug reactions were reported in either group in Step I or Step II. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

[25] Allowing for patients found ineligible at screening examination etc. before the start of study drug administration, about 3 reserve subjects per group were selected.
[26] Allowing for patients found ineligible at screening examination etc. before the start of study drug administration, about 3 reserve subjects per group were selected.

4.(iii).A.(1).3) Pharmacokinetic study in foreign subjects with renal impairment【5.3.3.3-01, Study Hi-[redacted]-105 ([redacted] 20[redacted] to [redacted] 20[redacted])】

An open-label study was conducted at 3 centers overseas to evaluate the tolerability, safety, and pharmacokinetics of peramivir in foreign subjects with renal impairment[27] (Target sample size of 30).

Subjects with normal renal function (Cohort 1), subjects with mild renal impairment (Cohort 2), subjects with moderate renal impairment (Cohort 3), and subjects with severe renal impairment (Cohort 4) were to receive a single intravenous dose of peramivir 2 mg/kg. Subjects with end-stage renal disease requiring chronic hemodialysis (Cohort 5) were to receive a single intravenous dose of peramivir 2 mg/kg (the first dose) at 2 hours prior to the start of dialysis, undergo at least a 10-day washout period, and then receive a single intravenous dose of peramivir 2 mg/kg (the second dose) immediately after the completion of dialysis.

All of the 30 subjects enrolled into the study (6 subjects per cohort) were included in the safety analysis population.

Adverse events occurred in 4 subjects (5 events) (retinal detachment, injection site reaction, cardiac murmur, headache, somnolence) in Cohort 1, 4 subjects (7 events) (queasy, vomiting, urinary sediment present, pain in extremity, facial neuralgia, dysmenorrhoea, headache) in Cohort 2, 2 subjects (4 events) (diarrhoea [3], gout [1]) in Cohort 3, 4 subjects (8 events) (diarrhoea, fatigability, nasopharyngitis, tooth abscess, hypoglycaemia, dizziness, headache, hypertension) in Cohort 4, and 1 subject (1 event) (skin lesion) in Cohort 5 (the second dose), and 1 subject (1 event) (hypotension) in Cohort 5 (the first dose). Adverse drug reactions reported include somnolence in Cohort 1, facial neuralgia and pain in extremity in Cohort 2, diarrhoea [1] and gout in Cohort 3, and nasopharyngitis and headache in Cohort 4.

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(iii).A.(1).4) Pharmacokinetic study in foreign healthy elderly subjects【5.3.3.3-02, Study Hi-[redacted]-104 ([redacted] 20[redacted] to [redacted] 20[redacted])】

[27] The degree of renal impairment was classified according to CL_{cr} calculated using the Cockcroft-Gault formula as follows: normal (CL_{cr} > 80 mL/min), mild renal impairment (CL_{cr} 50-80 mL/min), moderate renal impairment (CL_{cr} 30-49 mL/min), severe renal impairment (CL_{cr} < 30 mL/min), and end-stage renal disease (requiring chronic hemodialysis)

A randomized, double-blind, placebo-controlled study was conducted at a single center overseas to evaluate the tolerability, safety, and pharmacokinetics of peramivir in foreign healthy elderly subjects (≥ 65 years of age) [Target sample size of 20 (Part I, 20 subjects; Part II, 16 subjects [6 subjects each in the peramivir groups, 2 subjects each in the placebo groups])].

In Part I, peramivir 4 mg/kg was to be intravenously administered BID for 1 day. As initially specified, 3 subjects with urine protein of ≥ 150 mg per 24 hours from Day 1 to Day 2[28] were excluded from among the subjects enrolled in Part I and of the remaining 17 subjects, 16 subjects[29] entered Part II. In Part II, peramivir 4 mg/kg or placebo was to be intravenously administered BID for 5 days (Group A) or 10 days (Group B).

All of the 20 subjects enrolled into the study (Part I, 20 subjects; Part II, 16 subjects) were included in the safety analysis population.

Regarding safety, adverse events occurred in 5 subjects (5 events) (blood pressure increased [2], electrocardiogram QT corrected interval prolonged [1], diarrhoea [1], somnolence [1]) in Part I. In Group A of Part II, adverse events occurred in 5 subjects treated with peramivir (9 events) (diarrhoea [3], constipation [2], vessel puncture site bruise [1], headache [1], blood pressure increased [1], electrocardiogram QT corrected interval prolonged [1]) and 1 subject treated with placebo (2 events) (constipation [1], dysuria [1]). In Group B of Part II, adverse events occurred in 4 subjects treated with peramivir (10 events) (headache [2], electrocardiogram QT corrected interval prolonged [2], hunger [1], somnolence [1], bundle branch block left [1], flatulence [1], shoulder pain [1], upper respiratory tract infection [1]) and 2 subjects treated with placebo (4 events) (atrioventricular block first degree [1], myalgia [1], upper respiratory tract infection [1], blood pressure increased [1]). In Part I, 1 adverse drug reaction (somnolence) occurred in 1 subject and in Part II, 1 adverse drug reaction (somnolence) occurred with peramivir in Group B and 1 adverse drug reaction (myalgia) occurred with placebo in Group B. Of the 4 subjects who did not enter Part II from Part I, 2 subjects experienced adverse events after study discontinuation (haematuria [1], pharyngolaryngeal pain [1]). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(iii).A.(1).5) Thorough QT/QTc study in foreign healthy adult subjects【5.3.4.1-01, Study BCX1812-106 ([redacted] to [redacted])】

A randomized, double-blind, placebo- and positive-controlled, four-period crossover study was

[28] All of the 3 subjects already had urine protein of ≥ 150 mg per 24 hours before study drug administration.
[29] Since the target sample size was 16, one subject did not enter Part II.

conducted at a single center overseas to evaluate the effects of peramivir on the QT/QTc interval in foreign healthy adult subjects (Target sample size of 52).

Subjects were to receive each of the following treatments: Treatment A (a single intravenous dose of peramivir 600 mg and a single oral dose of MFLX placebo), Treatment B (a single intravenous dose of peramivir 1200 mg and a single oral dose of MFLX placebo), Treatment C (a single intravenous dose of peramivir placebo and a single oral dose of MFLX placebo), and Treatment D (a single oral dose of MFLX 400 mg and a single intravenous dose of peramivir placebo).

All of the 52 subjects enrolled into the study (the number of subjects treated with the study drug, Treatment A, 49 subjects; Treatment B, 50 subjects; Treatment C, 51 subjects; Treatment D, 52 subjects) were included in the ECG analysis population and in the safety analysis population.

Treatment A and Treatment B had no QTc interval prolongation effects and other repolarization abnormalities also did not occur.

Adverse events occurred in 3 subjects (4 events) (injection site haematoma [1], nasopharyngitis [1], oropharyngeal pain [1], dermatitis contact [1]) during Treatment A, 4 subjects (4 events) (anaemia [1], contusion [1], tremor [1], oropharyngeal pain [1]) during Treatment B, 6 subjects (8 events) (nausea [1], otitis externa [1], dizziness [1], dysuria [1], epistaxis [1], nasal congestion [1], oropharyngeal pain [1], rhinorrhoea [1]) during Treatment C, and 8 subjects (14 events) (injection site haematoma [3], feeling hot [2], injection site pain [2], dysmenorrhoea [2], dermatitis contact [2], nausea [1], injection site haemorrhage [1], metrorrhagia [1]) during Treatment D. Adverse drug reactions occurred in 2 subjects (2 events) (nausea [1], dizziness [1]) during Treatment C and 2 subjects (2 events) (nausea [1], feeling hot [1]) during Treatment D. One adverse event leading to treatment discontinuation (anaemia) occurred during Treatment B. There were no deaths or serious adverse events.

4.(iii).A.(1).6) Intramuscular pharmacokinetic study in foreign healthy adult subjects 【5.3.3.4-01, Study Him-[redacted]-111 ([redacted] 20[redacted] to [redacted] 20[redacted])】

An open-label, three-treatment, three-period crossover study in foreign healthy adult subjects (Target sample size of 27) was conducted at a single center overseas to evaluate the tolerability, safety, and pharmacokinetics of a single intravenous dose of peramivir, a single intramuscular dose of peramivir, and a single intramuscular dose of peramivir in combination with oral probenecid in each dose cohort.

Peramivir 75, 150, and 300 mg were to be administered as a single intravenous dose (Treatment A), as a single intramuscular dose (Treatment B), and as a single intramuscular dose + oral probenecid 1 g (Treatment C). Cohort 1 consisted of the peramivir 75 mg groups of Treatments A, B, and C, Cohort 2 consisted of the peramivir 150 mg groups of Treatments A, B, and C, and Cohort 3 consisted of the peramivir 300 mg groups of Treatments A, B, and C.

All of the 27 subjects enrolled into the study received at least one dose of study drug[30] and were included in the safety analysis population.

Regarding safety, adverse events occurred in 36% (9 of 25 subjects) of Cohort 1, 48% (12 of 25 subjects) of Cohort 2, and 69% (18 of 26 subjects) of Cohort 3. Adverse events occurring at least twice in each cohort were upper respiratory tract infection [2], headache [2], and nasal congestion [2] in Cohort 1, headache [5], dizziness [3], anorexia [2], somnolence [2], and syncope vagovagal [2] in Cohort 2, and blood CK increased [12] in Cohort 3. Adverse drug reactions occurred in 8% (2 of 25 subjects) of Cohort 1, in 24% (6 of 25 subjects) of Cohort 2, and in 12% (3 of 26 subjects) of Cohort 3. Adverse drug reactions occurring at least twice were headache [3], anorexia [2], and somnolence [2] in Cohort 2. No serious adverse events or deaths were reported.

4.(iii).A.(2) Phase II study

4.(iii).A.(2).1) Japanese phase II study in patients with seasonal influenza virus infection 【5.3.5.1-01, Study [redacted]22T0621 ([redacted] 20[redacted] to [redacted] 20[redacted])】

A double-blind, placebo-controlled study was conducted at 75 centers in Japan to evaluate the efficacy and safety of peramivir in Japanese patients with influenza virus infection [Target sample size of 240 (80 subjects in the peramivir 300 mg group, 80 subjects in the peramivir 600 mg group, 80 subjects in the placebo group)].

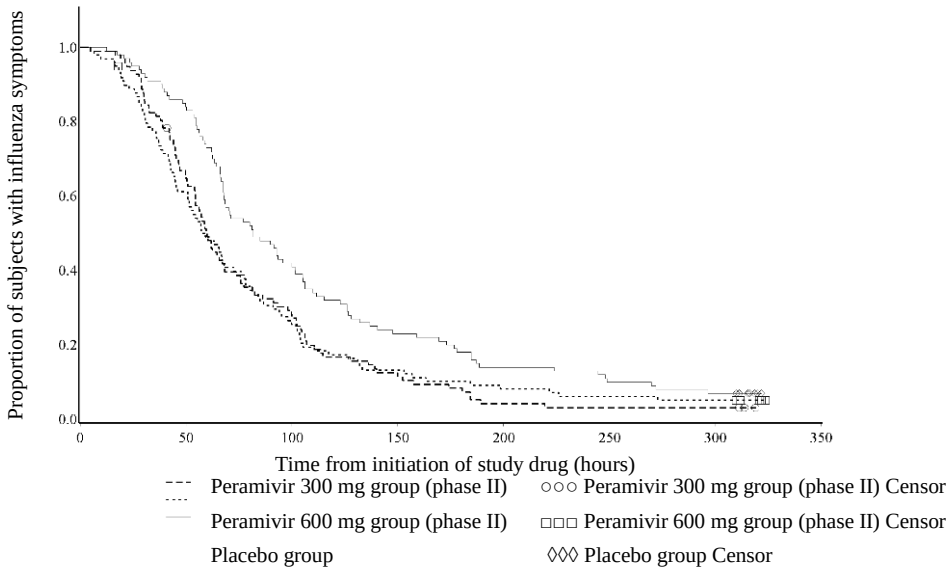
A single intravenous dose of peramivir 300 mg, 600 mg, or placebo was to be administered.

Of the 300 subjects enrolled into the study, 298 subjects (99 subjects in the peramivir 300 mg group, 99 subjects in the peramivir 600 mg group, 100 subjects in the placebo group) were included in the safety analysis population and remaining 2 subjects (untreated) were excluded.

[30] Three of the 27 subjects discontinued study medication before completing all treatments (intravenous peramivir, intramuscular peramivir, intramuscular peramivir + probenecid). Of whom, 2 subjects discontinued study medication for family reasons and 1 subject discontinued study medication due to consent withdrawal. There was no discontinuation due to adverse events.

The efficacy analysis population (Intention-To-Treat Infected: ITTI) included 296 subjects from among the safety analysis population (99 subjects in the peramivir 300 mg group, 97 subjects in the peramivir 600 mg group, 100 subjects in the placebo group) and excluded 2 subjects (1 case having unconfirmed influenza and 1 case with no efficacy data).

The primary efficacy endpoint of the median time to alleviation of symptoms (95% confidence interval [CI]) was 59.1 hours (50.9, 72.4) in the peramivir 300 mg group, 59.9 hours (54.4, 68.1) in the peramivir 600 mg group, and 81.8 hours (68.0, 101.5) in the placebo group. The Kaplan-Meier curve of the time to alleviation of symptoms for each group is presented in the following figure. The hazard ratio (95% CI) was 0.681 (0.511, 0.909) for peramivir 300 mg vs. placebo and 0.666 (0.499, 0.890) for peramivir 600 mg vs. placebo. Both of the peramivir groups achieved significant differences from placebo (Cox proportional hazards model, the adjusted one-sided *P*-value was 0.0046 for both groups).



Kaplan-Meier curve of time to alleviation of symptoms (ITTI)

Regarding safety, adverse events occurred in 87.9% (87 of 99 subjects) of the peramivir 300 mg group, 90.9% (90 of 99 subjects) of the peramivir 600 mg group, and 91.0% (91 of 100 subjects) of the placebo group and adverse drug reactions occurred in 52.5% (52 of 99 subjects) of the peramivir 300 mg group, 56.6% (56 of 99 subjects) of the peramivir 600 mg group, and 51.0% (51 of 100 subjects) of the placebo group. Only 1 adverse event leading to treatment discontinuation (cough) was reported in the placebo group. Adverse events or adverse drug reactions reported by at least 5% of subjects in any group were as shown in the following table.

Adverse events or adverse drug reactions reported by at least 5% of subjects in any group

System organ class	Preferred term	Adverse event			Adverse drug reaction		
		Peramivir 300 mg (N = 99)	Peramivir 600 mg (N = 99)	Placebo (N = 100)	Peramivir 300 mg (N = 99)	Peramivir 600 mg (N = 99)	Placebo (N = 100)
		No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)
Gastrointestinal disorders	Diarrhoea	14 (14.1)	15 (15.2)	17 (17.0)	11 (11.1)	10 (10.1)	11 (11.0)
	Nausea	3 (3.0)	6 (6.1)	1 (1.0)	2 (2.0)	4 (4.0)	1 (1.0)
Infections and infestations	Nasopharyngitis	0 (0.0)	4 (4.0)	6 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	Monocyte percentage increased	20 (20.2)	18 (18.2)	31 (31.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Blood glucose increased	18 (18.2)	17 (17.2)	18 (18.0)	5 (5.1)	4 (4.0)	2 (2.0)
	Protein urine present	9 (9.1)	11 (11.1)	18 (18.0)	6 (6.1)	7 (7.1)	10 (10.0)
	Urine β2MG increased	14 (14.1)	8 (8.1)	11 (11.0)	12 (12.1)	7 (7.1)	10 (10.0)
	Lymphocyte percentage increased	14 (14.1)	14 (14.1)	5 (5.0)	6 (6.1)	5 (5.1)	2 (2.0)
	White blood cells urine positive	8 (8.1)	9 (9.1)	8 (8.0)	1 (1.0)	3 (3.0)	2 (2.0)
	Blood bilirubin increased	7 (7.1)	8 (8.1)	7 (7.0)	3 (3.0)	4 (4.0)	4 (4.0)
	Lymphocyte morphology abnormal	11 (11.1)	4 (4.0)	6 (6.0)	5 (5.1)	1 (1.0)	1 (1.0)
	White blood cell count decreased	9 (9.1)	7 (7.1)	4 (4.0)	7 (7.1)	4 (4.0)	2 (2.0)
	ALT increased	4 (4.0)	7 (7.1)	8 (8.0)	2 (2.0)	7 (7.1)	4 (4.0)
	NAG increased	9 (9.1)	5 (5.1)	5 (5.0)	7 (7.1)	5 (5.1)	5 (5.0)
	Urine α1MG increased	6 (6.1)	6 (6.1)	6 (6.0)	5 (5.1)	6 (6.1)	6 (6.0)
	Albumin urine present	5 (5.1)	5 (5.1)	6 (6.0)	5 (5.1)	5 (5.1)	5 (5.0)
	AST increased	1 (1.0)	7 (7.1)	6 (6.0)	1 (1.0)	7 (7.1)	4 (4.0)
	Protein total decreased	3 (3.0)	4 (4.0)	6 (6.0)	0 (0.0)	1 (1.0)	1 (1.0)
	Blood phosphorus increased	6 (6.1)	3 (3.0)	4 (4.0)	6 (6.1)	2 (2.0)	2 (2.0)
	Blood LDH increased	2 (2.0)	6 (6.1)	4 (4.0)	2 (2.0)	6 (6.1)	0 (0.0)
	Blood urea decreased	5 (5.1)	3 (3.0)	4 (4.0)	1 (1.0)	2 (2.0)	2 (2.0)
	Eosinophil percentage increased	4 (4.0)	5 (5.1)	3 (3.0)	1 (1.0)	3 (3.0)	1 (1.0)
	Blood glucose decreased	5 (5.1)	4 (4.0)	2 (2.0)	2 (2.0)	1 (1.0)	0 (0.0)
	Blood phosphorus decreased	5 (5.1)	1 (1.0)	2 (2.0)	4 (4.0)	0 (0.0)	1 (1.0)

Incidence (%): Number of subjects with event/total number of subjects in treatment group × 100

No serious adverse events or deaths were reported.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Phase III study in patients with seasonal influenza virus infection【5.3.5.1-02, Study [redacted]15T0631 ([redacted] 20[redacted] to [redacted] 20[redacted])】

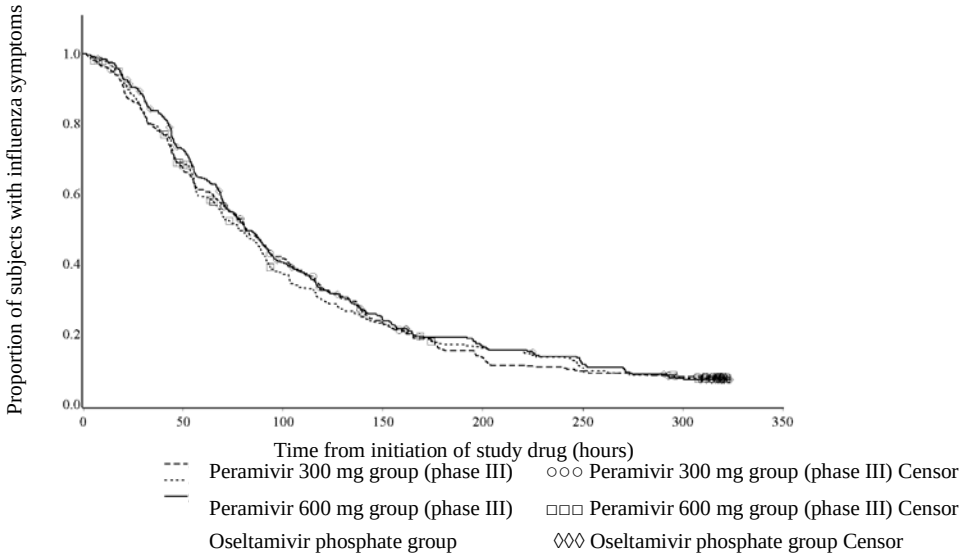
An double-blind, active-controlled study was conducted at 146 centers in the 3 countries of Japan, Korea, and Taiwan (100 centers in Japan, 25 centers in Korea, 21 centers in Taiwan) to evaluate the efficacy and safety of peramivir in patients with influenza virus infection [Target sample size of 1050 (350 subjects in the peramivir 300 mg group, 350 subjects in the peramivir 600 mg group, 350 subjects in the oseltamivir phosphate group)].

A single intravenous dose of peramivir 300 mg or 600 mg was to be administered for 1 day or oseltamivir phosphate 75 mg was to be orally administered BID for 5 days.

A non-inferiority margin of 1.170 for this study (hazard ratio for peramivir vs. oseltamivir phosphate) was chosen to prove that peramivir retains at least half of the effect of oseltamivir phosphate over placebo on the log hazard ratio scale, based on the hazard ratio of 0.73 for oseltamivir phosphate vs. placebo estimated from the analysis of 3 placebo-controlled clinical studies presented in the summary of the initial application for Tamiful®.

Of the 1099 subjects enrolled into the study (743 Japanese subjects, 250 Taiwanese subjects, 106 Korean subjects), 1093 subjects were included in the safety analysis population (364 subjects in the peramivir 300 mg group, 364 subjects in the peramivir 600 mg group, 365 subjects in the oseltamivir phosphate group) and the remaining 6 subjects (untreated) were excluded. The efficacy analysis population (Intention-To-Treat Infected: ITTI) included 1091 subjects from among the safety analysis population (364 subjects in the peramivir 300 mg group, 362 subjects in the peramivir 600 mg group, 365 subjects in the oseltamivir phosphate group) and excluded 2 subjects (cases with no efficacy data).

The primary efficacy endpoint of the median time to alleviation of symptoms (95% CI) was 78.0 hours (68.4, 88.6) in the peramivir 300 mg group, 81.0 hours (72.7, 91.5) in the peramivir 600 mg group, and 81.8 hours (73.2, 91.1) in the oseltamivir phosphate group. The Kaplan-Meier curve of the time to alleviation of symptoms for each group is presented in the following figure. The hazard ratio (97.5% CI) was 0.946 (0.793, 1.129) for peramivir 300 mg vs. oseltamivir phosphate and 0.970 (0.814, 1.157) for peramivir 600 mg vs. oseltamivir phosphate (Cox proportional hazards model). Because the upper bound of the 97.5% CI for both doses of peramivir in comparison to oseltamivir phosphate fell below the pre-specified non-inferiority margin, the non-inferiority of peramivir 300 mg and 600 mg to oseltamivir phosphate has been confirmed.



Kaplan-Meier curve of time to alleviation of symptoms (ITTI)

Regarding safety, adverse events occurred in 46.7% (170 of 364 subjects) of the peramivir 300 mg group, 47.8% (174 of 364 subjects) of the peramivir 600 mg group, and 48.8% (178 of 365 subjects) of the oseltamivir phosphate group and adverse drug reactions occurred in 14.0% (51 of 364 subjects) of the peramivir 300 mg group, 18.1% (66 of 364 subjects) of the peramivir 600 mg group, and 20.0% (73 of 365 subjects) of the oseltamivir phosphate group. Adverse events or adverse drug reactions reported by at least 5% of subjects in any group were as shown in the following table.

Adverse events or adverse drug reactions reported by at least 5% of subjects in any group

System organ class	Preferred term	Adverse event			Adverse drug reaction		
		Peramivir 300 mg (N = 364)	Peramivir 600 mg (N = 364)	Oseltamivir phosphate (N = 365)	Peramivir 300 mg (N = 364)	Peramivir 600 mg (N = 364)	Oseltamivir phosphate (N = 365)
		No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)
Gastrointestinal disorders	Diarrhoea	24 (6.6)	30 (8.2)	27 (7.4)	14 (3.8)	20 (5.5)	19 (5.2)
	Nausea	8 (2.2)	8 (2.2)	20 (5.5)	2 (0.5)	7 (1.9)	16 (4.4)
Investigations	Neutrophil count decreased	39 (10.7)	38 (10.4)	34 (9.3)	9 (2.5)	14 (3.8)	13 (3.6)
	Protein urine present	17 (4.7)	16 (4.4)	22 (6.0)	7 (1.9)	4 (1.1)	10 (2.7)

Incidence (%): Number of subjects with event/total number of subjects in treatment group × 100

Serious adverse events reported include bronchitis [1], influenza [1], pneumonia [1], and myalgia [1] in the peramivir 300 mg group and pneumonia [1] and vomiting [1] in the oseltamivir phosphate group, but a causal relationship to the study drug was denied for all

events except for vomiting [1] in the oseltamivir phosphate group. The outcomes of these events were all reported as resolved. Adverse events leading to treatment discontinuation occurred in 3 subjects (3 events) (salivary gland pain [1], bronchopneumonia [1], rash [1]) in the peramivir 300 mg group, 6 subjects (7 events) (abdominal pain upper [1], nasopharyngitis [1], pneumonia [1], arthralgia [1], drug eruption [1], rash [1], urticaria [1]) in the peramivir 600 mg group, and 5 subjects (6 events) (vomiting [2], nausea [1], pneumonia [1], upper respiratory tract infection [1], back pain [1]) in the oseltamivir phosphate group and a causal relationship to study drug was denied for these events other than rash [1] in the peramivir 300 mg group, abdominal pain upper [1], arthralgia [1], drug eruption [1], rash [1], and urticaria [1] in the peramivir 600 mg group, and vomiting [2], nausea [1], and back pain [1] in the oseltamivir phosphate group. No deaths were reported.

4.(iii).A.(3).2) Japanese phase III study in high-risk patients with seasonal influenza virus infection【5.3.5.2-01, Study [redacted]16T0632 ([redacted] 20[redacted] to [redacted] 20[redacted])】

A double-blind, uncontrolled study was conducted at 38 centers in Japan to evaluate the efficacy and safety of peramivir in high-risk Japanese patients[31] with influenza virus infection [Target sample size of ≥ 50 (25 subjects in the peramivir 300 mg group, 25 subjects in the peramivir 600 mg group)].

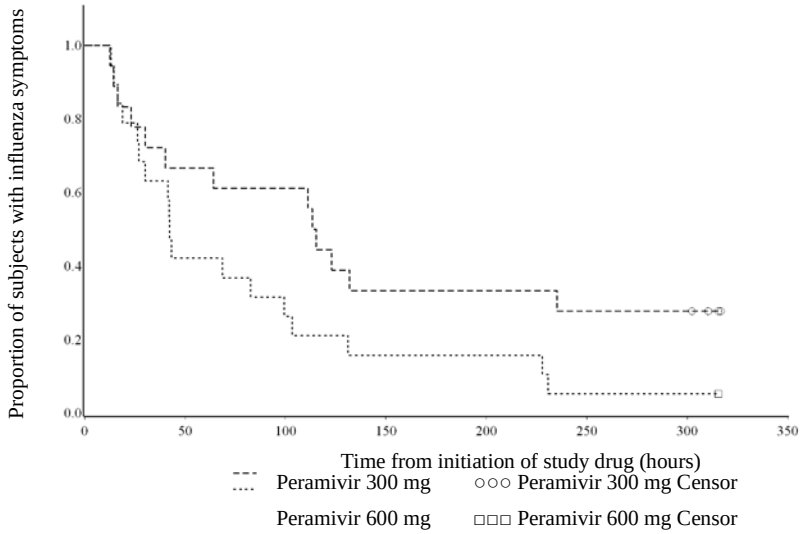
A single intravenous dose of peramivir 300 mg or 600 mg was to be administered and the duration of treatment was 1 to 5 days. The criteria for continuing treatment from Day 2 onward were as follows: “If body temperature is ≥ 37.5°C, treatment should be continued. If body temperature is < 37.5°C, treatment should be stopped as a rule. However, if treatment continuation is judged necessary by the investigator (sub-investigator) based on clinical symptoms, treatment may be continued.”

All of the 42 subjects enrolled into the study were included in the safety analysis population. A total of 37 subjects (18 subjects in the peramivir 300 mg group, 19 subjects in the peramivir 600 mg group) were included in the efficacy analysis population (Per-Protocol-Set: PPS) and 5 subjects (1 ineligible case and 4 protocol violation cases) were excluded.

The primary efficacy endpoint of the median time to alleviation of symptoms (90% CI) was 68.6 hours (41.5, 113.4) in the peramivir 300 mg and 600 mg groups combined, 114.4 hours (40.2, 235.3) in the peramivir 300 mg group, and 42.3 hours (30.0, 82.7) in the peramivir 600

[31] Definition of high-risk patients: patients with poorly controlled diabetes, patients with chronic respiratory disease requiring pharmacotherapy, or patients currently on immunosuppressant medication

mg group and the hazard ratio (90% CI) for peramivir 600 mg vs. peramivir 300 mg was 0.497 (0.251, 0.984) (Cox proportional hazards model). The Kaplan-Meier curves of the time to alleviation of symptoms for the peramivir 300 mg and 600 mg groups are presented in the following figure. The median time to alleviation of symptoms (90% CI) was 92.0 hours (14.6, 235.3) in single-dosed subjects (N = 10) and 64.1 hours (41.5, 111.2) in multiple-dosed subjects (treated for 2 to 5 days) (N = 27).[32]



Kaplan-Meier curve of time to alleviation of symptoms (PPS)

Regarding safety, adverse events occurred in 71.4% (15 of 21 subjects) of the peramivir 300 mg group, 76.2% (16 of 21 subjects) of the peramivir 600 mg group, 63.6% (7 of 11 subjects) of the single-dosed subjects, and 77.4% (24 of 31 subjects) of the multiple-dosed subjects. Adverse drug reactions occurred in 28.6% (6 of 21 subjects) of the peramivir 300 mg group, 38.1% (8 of 21 subjects) of the peramivir 600 mg group, 9.1% (1 of 11 subjects) of the single-dosed subjects, and 41.9% (13 of 31 subjects) of the multiple-dosed subjects. Adverse events or adverse drug reactions reported by at least 5% of subjects in any group were as shown in the following table.

[32] No. of multiple-dosed subjects per group: Peramivir 300 mg group (2 days of treatment, 9 subjects; 3 days of treatment, 1 subject; 4 days of treatment, 0 subject; 5 days of treatment, 1 subject), Peramivir 600 mg group (2 days of treatment, 14 subjects; 3 days of treatment, 1 subject; 4 days of treatment, 1 subject; 5 days of treatment, 0 subject)

Adverse events or adverse drug reactions reported by at least 5% of subjects in any group

System organ class	Preferred term	Adverse event				Adverse drug reaction			
		Peramivir 300 mg (N = 21)	Peramivir 600 mg (N = 21)	Single dose (N = 11)	Multiple dose (N = 31)	Peramivir 300 mg (N = 21)	Peramivir 600 mg (N = 21)	Single dose (N = 11)	Multiple dose (N = 31)
		No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)	No. of subjects with event (%)
Gastrointestinal disorders	Stomatitis	2 (9.5)	0 (0.0)	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	Pneumonia	1 (4.8)	2 (9.5)	0 (0.0)	3 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Oral herpes	1 (4.8)	2 (9.5)	2 (18.2)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	Blood glucose increased	6 (28.6)	4 (19.0)	2 (18.2)	8 (25.8)	2 (9.5)	1 (4.8)	0 (0.0)	3 (9.7)
	Eosinophil count increased	3 (14.3)	1 (4.8)	0 (0.0)	4 (12.9)	1 (4.8)	0 (0.0)	0 (0.0)	1 (3.2)
	Glucose urine present	1 (4.8)	3 (14.3)	2 (18.2)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Neutrophil count decreased	4 (19.0)	1 (4.8)	1 (9.1)	4 (12.9)	3 (14.3)	0 (0.0)	1 (9.1)	2 (6.5)
	Protein total decreased	3 (14.3)	1 (4.8)	1 (9.1)	3 (9.7)	1 (4.8)	0 (0.0)	0 (0.0)	1 (3.2)
	White blood cells urine positive	2 (9.5)	1 (4.8)	1 (9.1)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Blood phosphorus decreased	2 (9.5)	2 (9.5)	0 (0.0)	4 (12.9)	1 (4.8)	0 (0.0)	0 (0.0)	1 (3.2)
	Urine ketone body present	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)

Incidence (%): Number of subjects with event/total number of subjects in treatment group × 100

There were no adverse events leading to treatment discontinuation. Serious adverse events reported include bacterial pneumonia [1] in the peramivir 300 mg group (3-day treatment) and pneumonia [1] in the peramivir 600 mg group (2-day treatment). A causal relationship to the study drug was denied for both events and the outcomes of these events were reported as improved and resolved, respectively. No deaths were reported.

4.(iii).B *Outline of the review by PMDA*

4.(iii).B.(1) Efficacy

For efficacy evaluation of peramivir, PMDA mainly reviewed the data from controlled clinical studies, i.e., a Japanese phase II study (Study [redacted]22T0621) and a multiregional phase III study (Study [redacted]15T0631). Using the data from a Japanese phase III study in high-risk patients with influenza virus infection (Study [redacted]16T0632), the relationship of the dose and the number of doses received to the efficacy of peramivir was investigated.

4.(iii).B.(1).1) Use of foreign data

The applicant explained the reason for considering that the use of pooled data from Japanese, Taiwanese, and Korean patients enrolled in a multiregional phase III study is appropriate, as follows:

According to the results of foreign phase I studies (Studies Hi-[redacted]-101 and Hi-[redacted]-102) and

Japanese phase I studies (Studies [redacted]12T0611 and [redacted]14T0612), the pharmacokinetics of peramivir are similar between Japanese and foreign healthy adult subjects and peramivir is mostly excreted unchanged in urine [see 4.(ii) Summary of clinical pharmacology studies]. Therefore, peramivir is characterized as ethnically insensitive. In addition, since the pharmacokinetic data from the multiregional phase III study demonstrated no clinically meaningful ethnic differences [see 4.(ii) Summary of clinical pharmacology studies], the Taiwanese and Korean data can be used.

PMDA largely accepted the applicant's explanation.

PMDA considers that there is no problem with the use of the time to alleviation of symptoms as the primary efficacy endpoint. Meanwhile, PMDA asked the applicant to explain the measures to ensure that the criteria used to determine the resolution of influenza symptoms do not vary among the ethnic groups and discuss possible ethnic differences based on the obtained results.

The applicant responded as follows:
The time to alleviation of symptoms was assessed based on the patient's subjective influenza symptoms (7 symptoms) using the patient diary. When a clinical trial involving different ethnic groups is conducted, and if the assessment method and patients' perception of their symptoms differ among the ethnic groups, the trial may raise a concern about a lack of the uniformity of efficacy evaluation. Therefore, the items of patient diary were chosen in accordance with an international standard influenza symptom severity scale, the Influenza Symptom Severity (ISS) scale, which had been used in multiregional studies of oseltamivir phosphate and zanamivir hydrate. In order to ensure the uniformity of evaluation in the multiregional phase III study, based on the Japanese version of the ISS scale used in a Japanese phase II study, each local language version of the ISS scale was prepared, under the supervision of Dr. R. H. Osborne who developed the ISS scale, through the following elaborate procedures: (1) translation into local languages by proficient translators, (2) checking by local clinical trial staff [multiple staff members], (3) back-translation by proficient translators, and (4) final checking by the sponsor. The time to alleviation of symptoms in the multiregional phase III study was analyzed using Cox proportional hazards model including current smoking status, total score of 7 symptoms of influenza at baseline, country (region), influenza viral type, gender, complications, and prior therapy status as covariates. With respect to the effect of country (region), there were significant differences between Japan and Korea (P = 0.0353) and the time to alleviation of symptoms was shorter in Korean subjects than in Japanese subjects. When the background factors of Japanese and Korean subjects were assessed, the distribution of influenza subtypes was found to be

significantly different between Japanese and Korean subjects (Japanese subjects, A/H1N1, 56.3%, A/H3N2, 25.9%; Korean subjects, A/H1N1, 16.1%, A/H3N2, 69.5%) and subgroup analysis showed that the time to alleviation of symptoms was about 15 hours shorter in subjects infected with A/H3N2 subtype viruses compared with those infected with A/H1N1 subtype viruses. Therefore, the differences in the time to alleviation of symptoms between Japan and Korea were attributable to an imbalance in the distribution of influenza viral subtypes and not to ethnic differences in the criteria used to determine the resolution of influenza symptoms.

Furthermore, PMDA asked the applicant to explain the efficacy data by country (region), as such data had not been submitted.

The applicant responded as follows:
The time to alleviation of symptoms by country (region) was analyzed. As a result, there were no statistically significant differences among the oseltamivir phosphate, peramivir 300 mg, and peramivir 600 mg groups in Japan, Korea, or Taiwan (see the table below). In order to assess whether the size of the effect of peramivir compared with oseltamivir phosphate differs according to country (region), the interaction effect between country (region) and treatment group was tested using Cox proportional hazards model. As a result, $P = 0.6041$ was given and no statistically significant differences were found. In Korea, the time to alleviation of symptoms was shorter in all groups and the hazard ratio was > 1 for both the peramivir 300 mg and 600 mg groups, showing a different trend from the overall data and the data from other countries (region). This result was possibly due to the small number of subjects in Korea, thus affecting the estimated hazard ratio.

The above results indicate that there are no differences in the efficacy of peramivir among the countries (region).

Analysis of time to alleviation of symptoms by country (region) (ITTI)

	Japan			Korea		
	Peramivir 300 mg N = 247	Peramivir 600 mg N = 249	Oseltamivir phosphate N = 246	Peramivir 300 mg N = 36	Peramivir 600 mg N = 34	Oseltamivir phosphate N = 35
Time to alleviation of symptoms						
Median (hours)	78.0	80.7	80.6	68.4	49.7	63.4
95% CI	68.1, 88.6	71.1, 91.3	70.0, 92.3	43.5, 119.0	31.1, 103.0	37.6, 86.8
Difference from oseltamivir phosphate (hours)	-2.6	0.1	-	5.0	-13.7	-
Hazard ratio	0.916	0.946	-	1.349	1.196	-
97.5% CI	0.740, 1.135	0.764, 1.171	-	0.733, 2.482	0.635, 2.252	-
P-value (two-sided)*	0.3598	0.5583	-	0.2714	0.5263	-
	Taiwan			Overall		
	Peramivir	Peramivir	Oseltamivir	Peramivir	Peramivir	Oseltamivir

	300 mg N = 81	600 mg N = 79	phosphate N = 84	300 mg N = 364	600 mg N = 362	phosphate N = 365
Time to alleviation of symptoms						
Median (hours)	80.0	104.0	103.4	78.0	81.0	81.8
95% CI	57.4, 107.8	72.2, 150.1	77.2, 137.2	68.4, 88.6	72.7, 91.5	73.2, 91.1
Difference from oseltamivir phosphate (hours)	-23.5	0.6	-	-3.8	-0.8	-
Hazard ratio	0.939	0.969	-	0.946	0.970	-
97.5% CI	0.628, 1.402	0.658, 1.426	-	0.793, 1.129	0.814, 1.157	-
P-value (two-sided)*	0.7234	0.8556	-	0.4836	0.7015	-

Analysis method: Cox proportional hazards model
Covariates: current smoking status, total score of influenza symptoms at baseline, influenza viral type, gender, complications, prior therapy status
*: vs. oseltamivir phosphate

PMDA considers as follows:

Because Cox proportional hazard analysis revealed no interaction effect between country (region) and treatment group and the difference from oseltamivir phosphate in the median time to alleviation of symptoms was largely consistent among the countries (region), the size of the effect of peramivir compared with oseltamivir phosphate does not differ according to country (region).

Based on the above, PMDA concluded that there is no particular problem with evaluating the efficacy of peramivir based on the multiregional phase III study data containing foreign data.

4.(iii).B.(1).2) Efficacy evaluation

(a) Efficacy of peramivir

The times to alleviation of symptoms in Japanese phase II and multiregional phase III studies were as shown below.

The results of analysis of time to alleviation of symptoms in Japanese phase II study (ITTI)

	Peramivir 300 mg N = 99	Peramivir 600 mg N = 97	Placebo N = 100
Median (hours)	59.1	59.9	81.8
95% CI	50.9, 72.4	54.4, 68.1	68.0, 101.5
Difference from placebo (hours)	-22.7	-21.9	-
Cox proportional hazards model			
Estimate	-0.3837	-0.4062	-
Standard error (SE)	0.1472	0.1479	-
Hazard ratio	0.681	0.666	-
95% CI	0.511, 0.909	0.499, 0.890	-
Chi-square statistic	6.7916	7.5463	-
Degree of freedom	1	1	-
P-value (one-sided)	0.0046*	0.0030*	-
Adjusted *P*-value (one-sided)	0.0046*	0.0046*	-

Analysis method: Cox proportional hazards model
Covariates: current smoking status, total score of influenza symptoms at baseline
Adjusted *P*-value: Adjusted by the Hochberg method
*: One-sided level of significance of 0.025

The results of analysis of time to alleviation of symptoms in multiregional phase III study (ITTI)

	Peramivir 300 mg N = 364	Peramivir 600 mg N = 362	Oseltamivir phosphate N = 365
Median (hours)	78.0	81.0	81.8
95% CI	68.4, 88.6	72.7, 91.5	73.2, 91.1
Difference from oseltamivir phosphate (hours)	-3.8	-0.8	-
Cox proportional hazards model			
Estimate	-0.0552	-0.0301	-
SE	0.0788	0.0786	-
Hazard ratio	0.946	0.970	-
97.5% CI	0.793, 1.129	0.814, 1.157	-
P-value (two-sided)	0.4836	0.7015	-

Analysis method: Cox proportional hazards model
Covariates: current smoking status, total score of influenza symptoms at baseline, country (region), influenza viral type, gender, complications, prior therapy status

The applicant explained as follows:

Because the time to alleviation of symptoms was reduced significantly in the peramivir 300 mg and 600 mg groups compared with the placebo group in the Japanese phase II study, the efficacy of peramivir against influenza virus infection was confirmed. The median times to alleviation of symptoms in the Japanese phase II and multiregional phase III studies were 59.1 hours and 78.0 hours, respectively, in the peramivir 300 mg groups, and 59.9 hours and 81.0 hours, respectively, in the peramivir 600 mg groups, showing that the times to alleviation of symptoms in the both groups were about 20 hours longer in the multiregional phase III study compared with the Japanese phase II study. Meanwhile, in 3 placebo-controlled clinical studies conducted for the development of oseltamivir phosphate, there was a difference of about 17 hours in the median time to alleviation of symptoms in the oseltamivir phosphate group (Study JV15823, 70.0 hours; Study WV15670, 87.4 hours; Study WV15671, 71.5 hours). Given this finding, the median time to alleviation of symptoms of 81.8 hours in the oseltamivir phosphate group in the multiregional phase III study should be within the year-to-year variability. Accordingly, it seems that the multiregional phase III study also demonstrated the efficacy of oseltamivir phosphate as an active control against influenza virus infection and confirmed the non-inferiority of peramivir to oseltamivir phosphate, thus indicating the efficacy of peramivir.

PMDA considers as follows:

It is understood that the time to alleviation of symptoms may vary from study to study, as the type of circulating viruses differs according to the year or geographic location of clinical trial. However, there is little basis for concluding that the efficacy of oseltamivir phosphate as an active control has been demonstrated also in the multiregional phase III study just because the time to alleviation of symptoms in the oseltamivir phosphate group in the multiregional phase III study was within its variability across 3 clinical studies conducted for the development of oseltamivir phosphate.

On the other hand, there is no objection to the multiregional phase III study designed to include oseltamivir phosphate, which is widely used in clinical practice, as a comparator, but if a placebo group was included in the study, the efficacy of peramivir may have been confirmed more clearly. However, the times to alleviation of symptoms in the peramivir 300 mg and 600 mg groups were both about 20 hours longer in the multiregional phase III study than in the Japanese phase II study and there was no difference in the time to alleviation of symptoms between the placebo group of the Japanese phase II study and the oseltamivir group of the multiregional phase III study (both 81.8 hours). Thus, it can not be ruled out that the efficacy of oseltamivir phosphate and peramivir was diminished for some reasons during the flu season of the multiregional phase III study.

Concerning influenza viruses circulating during the flu season of the multiregional phase III study ([redacted] 20[redacted] to [redacted] 20[redacted]), the following findings were noted: (a) most of the A/H1N1 subtype viruses were resistant to oseltamivir (Infectious Agents Surveillance Report (IASR), Infectious Disease Surveillance Center, National Institute of Infectious Diseases: Seasonal influenza (A/H1N1) virus resistance to oseltamivir, 2008/2009 season [http://idsc.nih.go.jp/iasr/rapid/pr3503.html]); and (b) the A/H1N1 subtype accounted for 54.8% (598 of 1091 patients) of the viruses isolated and identified in this study and these specimens were sequenced, where possible, and 99.8% (483 of 484 specimens) of the sequenced specimens had the H275Y NA mutation associated with oseltamivir resistance (H275Y mutant virus) [see 3.(i).B.(1) NA inhibitory activity for clinical isolates from clinical studies]. Therefore, PMDA considered that a detailed review of efficacy evaluation in this study, including the possibility of diminished efficacy of oseltamivir phosphate as a comparator, is needed and asked the applicant to explain the clinical efficacy of oseltamivir phosphate against the H275Y mutant virus based on the findings including published literature and guidelines in Japan and overseas.

The applicant responded as follows:
The US Centers for Disease Control and Prevention (CDC)'s recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season[33] and WHO (World Health Organization) guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses[34] advise against the use of oseltamivir phosphate for H275Y mutant virus infection. On the other hand, the second edition

[33] Update interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season (September 22, 2009)
[34] WHO guidelines for pharmacological management of Pandemic (H1N1) 2009 influenza and other influenza viruses (August 20, 2009)

of the recommendation titled “How to respond to novel influenza in general practice” issued by the Japanese Association for Infectious Diseases[35] states that “although resistant strains of H1N1 virus (“Russian flu”) have emerged frequently, these strains show *in vitro* resistance and oseltamivir is considered still effective in clinical use”[36] and the positioning of oseltamivir phosphate for H275Y mutant virus infection is different between Japan and overseas. In these guidelines, however, there are no clinical data showing the effect of oseltamivir phosphate against the H275Y mutant virus. There was a published article investigating the clinical effectiveness of oseltamivir phosphate against the H275Y mutant virus.[37]

PMDA considers as follows:

The published article cited by the applicant (J Infect 2009; 59: 207-212) compared 44 patients infected with influenza A/H1N1 viruses without the H275Y mutation during the 2007-2008 season with 29 patients infected with influenza A/H1N1 viruses with the H275Y mutation during the 2008-2009 season. As a result, the clinical efficacy of oseltamivir phosphate against the 2008-2009 season’s A/H1N1 virus compared with the 2007-2008 season’s virus was diminished especially in children, which may have been attributed to the H275Y mutation, resulting in a conclusion that the use of oseltamivir phosphate is not recommended for children and high-risk patients with H275Y mutant virus infection. However, although the above article indicates that the H275Y mutation may be associated with diminished efficacy of oseltamivir phosphate, as no placebo control group was included for both seasons, it is difficult to determine based on these results that oseltamivir phosphate is clinically ineffective against H275Y mutant virus infection. In addition, the Japanese and overseas guidelines have different opinions on the efficacy of oseltamivir phosphate against the H275Y mutant virus and at present, there is no definitive evidence for the clinical efficacy of oseltamivir phosphate against the H275Y mutant virus. In order to determine the clinical efficacy, further evidence for efficacy needs to be accumulated, such as by conducting a placebo-controlled comparative study.

Based on the above, PMDA considers as follows:

Although the multiregional phase III study has confirmed the non-inferiority of peramivir to oseltamivir phosphate, most of the viral isolates from the subgroup of patients with A/H1N1 virus infections, which accounted for 54.8% (598 of 1091 patients) of the overall population, had the H275Y mutation. Since the efficacy of oseltamivir phosphate against the H275Y mutant virus is undefined, the efficacy of peramivir against the H275Y mutant virus is also undefined.

[35] The recommendations from the Japanese Association for Infectious Diseases, the second edition of “How to respond to novel influenza in general practice” (September 15, 2009)

[36] 【Note by PMDA】 No evidence (e.g. references) is presented in the original.

[37] J Infect 2009 ; 59: 207-212

On the other hand, since the Japanese phase II study has confirmed the superiority of peramivir over placebo, based on a comprehensive judgment of the obtained results, it is concluded that the efficacy of peramivir against influenza virus infection has been confirmed, except that the efficacy of peramivir against infections caused by some strains of viruses with an amino acid substitution in NA, e.g., the H275Y mutant virus, is undefined.

(b) Efficacy evaluation by influenza viral type

The results of analysis of the time to alleviation of symptoms by influenza viral type in Japanese phase II and multiregional phase III studies were as shown below. In the Japanese phase II study, among the 296 subjects in the ITTI population, 293 subjects had type A influenza and 3 subjects had type B influenza (2 subjects in the peramivir 300 mg group, 1 subject in the peramivir 600 mg group, 0 subject in the placebo group).

Time to alleviation of symptoms by influenza viral type/subtype in Japanese phase II study (ITTI)

Influenza A/H1N1 subtype virus infection			
	Peramivir 300 mg N = 74	Peramivir 600 mg N = 69	Placebo N = 72
Median (hours)	52.5	62.6	81.4
95% CI	42.8, 65.8	56.5, 77.3	66.3, 99.9
Influenza A/H3N2 subtype virus infection			
	Peramivir 300 mg N = 21	Peramivir 600 mg N = 25	Placebo N = 24
Median (hours)	76.1	50.5	81.0
95% CI	53.4, 84.1	42.0, 81.4	67.3, 158.8

Analysis method: Cox proportional hazards model
Covariates: current smoking status, total score of influenza symptoms at baseline, country (region), gender, concomitant diseases, prior therapy status

Time to alleviation of symptoms by influenza viral type/subtype in multiregional phase III study (ITTI)

Influenza A/H1N1 subtype virus infection			
	Peramivir 300 mg N = 197	Peramivir 600 mg N = 200	Oseltamivir phosphate N = 201
Median (hours)	80.2	83.6	88.8
95% CI	69.3, 90.6	72.7, 101.9	73.1, 102.2
Influenza A/H3N2 subtype virus infection			
	Peramivir 300 mg N = 112	Peramivir 600 mg N = 108	Oseltamivir phosphate N = 108
Median (hours)	69.9	70.6	75.1
95% CI	54.4, 97.1	47.7, 91.9	63.4, 92.6
Type B influenza virus infection			
	Peramivir 300 mg N = 21	Peramivir 600 mg N = 26	Oseltamivir phosphate N = 23
Median (hours)	55.3	92.8	92.7
95% CI	43.9, 86.4	57.4, 116.1	70.2, 138.5

Analysis method: Cox proportional hazards model
Covariates: current smoking status, total score of influenza symptoms at baseline, country (region), gender, concomitant diseases, prior therapy status

i) Type A influenza virus infections

A/H1N1 subtype

In the 20[redacted]-20[redacted] season during which the multiregional phase III study was conducted,

H275Y-mutant pandemic influenza virus was reported and 54.8% of the overall study population (598 of 1091 patients) had influenza A/H1N1 subtype virus infections and most of the viral isolates possessed the H275Y mutation. On the other hand, in the flu season of the Japanese phase II study ([redacted] 20[redacted] to [redacted] 20[redacted]), the detection rate of influenza A/H1N1 virus strains with the H275Y mutation was low (2.6% [45 of 1734 strains]).[38] The NA inhibitory activity (mean IC_{50}) of oseltamivir carboxylate for the clinical isolates of influenza A/H1N1 virus from the multiregional phase III study was high at 87.7 (nmol/L), while the NA inhibitory activity (mean IC_{50}) of oseltamivir carboxylate in the Japanese phase II study was 2.56 (nmol/L) [see 3.(i).B.(1) NA inhibitory activity for clinical isolates from clinical studies]. Taking account of these findings, the H275Y mutant virus had little effect on the efficacy results of the Japanese phase II study.

Based on the above, as the Japanese phase II study has confirmed the superiority of peramivir over placebo and the median times to alleviation of symptoms in the treatment groups (52.5 hours in the peramivir 300 mg group, 62.6 hours in the peramivir 600 mg group, 81.4 hours in the placebo group) also indicate that peramivir is expected to achieve clinically significant reduction of the time to alleviation of symptoms, thereby showing the efficacy of peramivir against influenza A/H1N1 virus infections except for drug-resistant influenza A/H1N1 viruses, e.g., the H275Y mutant virus.

On the other hand, in the multiregional phase III study, most of the isolates from the enrolled patients with influenza A/H1N1 virus infections possessed the H275Y mutation and the times to alleviation of symptoms in the peramivir 300 mg and 600 mg groups in this study were about 20 hours longer compared to those in the Japanese phase II study from which very few resistant viruses were isolated. While the NA inhibitory activity (mean IC_{50}) of peramivir was 1.41 (nmol/L) in the Japanese phase II study, the NA inhibitory activity (mean IC_{50}) of peramivir for the clinical isolates of influenza A/H1N1 virus from the multiregional phase III study was high at 22.2 (nmol/L) [see 3.(i).B.(1) NA inhibitory activity for clinical isolates from clinical studies]. Thus, it cannot be ruled out that the H275Y mutant virus affected the efficacy results of peramivir. Consequently, a definitive conclusion on the efficacy of peramivir against the H275Y mutant virus cannot be drawn from the results of the multiregional phase III study, which leaves its clinical efficacy undefined. Since the clinical efficacy of NA inhibitors (including peramivir) against infections caused by influenza viruses with a mutation associated

[38] Infectious Agents Surveillance Report (IASR), Infectious Disease Surveillance Center, National Institute of Infectious Diseases: Influenza (A/H1N1) virus resistance to oseltamivir (H275Y*) in Japan [2nd report] (Vol. 29 p. 334-339: December 2008) <http://idsc.nih.go.jp/iasr/29/346/pr3462.html>

with resistance to NA inhibitors, e.g., H275Y mutation, is of major concern and can provide key information for selecting the drug, it is necessary to actively collect post-marketing information on the efficacy of peramivir against NA inhibitor-resistant influenza virus infections and provide information to the medical practice promptly when new evidence becomes available.

A/H3N2 subtype

PMDA considers that the efficacy of peramivir against influenza A/H3N2 virus infections is expected, based on the following reasons: (1) the issue of oseltamivir resistance of influenza viruses of any type/subtype other than A/H1N1 subtype was not specifically pointed out in the flu season during which the multiregional phase III study was conducted ([redacted] 20[redacted] to [redacted] 20[redacted]) [the Infectious Agents Surveillance Report (IASR) from the Infectious Disease Surveillance Center, National Institute of Infectious Diseases: "Flash report" Influenza (A/H1N1) virus resistance to oseltamivir (H275Y) in Japan, 2008/09 season (2nd report, March 23, 2009) http://idsc.nih.go.jp/iasr/rapid/pr3503.html][39]; (2) the results of the subgroup of patients infected with influenza viruses of A/H3N2 subtype in the Japanese phase II and multiregional phase III studies have been submitted; and (3) the NA inhibitory activities (mean IC_{50}) of peramivir for the clinical isolates of influenza A/H3N2 virus from the Japanese phase II and multinational phase III studies were 1.48 and 0.828 (nmol/L), respectively, which were similar to those of oseltamivir carboxylate and zanamivir [see 3.(i).B.(1) NA inhibitory activity for clinical isolates from clinical studies].

ii) Type B influenza virus infections

The median time to alleviation of symptoms in the subgroup of patients with type B influenza virus infections in the multiregional phase III study was 92.7 hours for the oseltamivir phosphate group, 55.3 hours for the peramivir 300 mg group, and 92.8 hours for the peramivir 600 mg group. Since the time to alleviation of symptoms was shorter in the peramivir 300 mg group than in the peramivir 600 mg group, PMDA asked the applicant to explain why the expected dose-response relationship was not shown.

The applicant responded as follows:

With respect to the dose-response relationship for the efficacy of peramivir against influenza virus infection, it had been expected from the results of the Japanese phase II study that

[39] Surveillance of NAI resistant strains of influenza A/H3N2 and B viruses was conducted and 86 stains of A/H3N2 subtype and 18 strains of B type isolated across Japan during the 2008/09 season were also tested for susceptibility to oseltamivir phosphate and zanamivir. As a result, among the A/H3N2 isolates from the 2008/09 season, only 1 strain exhibited about a 40-fold reduction in susceptibility to zanamivir and other strains were all sensitive to both drugs. The surveillance report states that there have to date been no reports of resistant strains of influenza A/H3N2 or B viruses isolated in foreign countries.

peramivir 600 mg would have comparable or greater efficacy than peramivir 300 mg. However, the outcome in the subgroup of patients with influenza B virus infections in the multiregional phase III study was not as expected. This was possibly due to the fact that the number of subjects in the subgroup of influenza B virus infections was as small as 70 subjects (21 subjects in the peramivir 300 mg group, 26 subjects in the peramivir 600 mg group, 23 subjects in the oseltamivir phosphate group), which was not large enough to evaluate differences between doses with adequate precision. The estimated hazard ratios (97.5% CI) for peramivir 300 mg and 600 mg vs. oseltamivir phosphate were 0.445 (0.202, 0.982) and 0.706 (0.341, 1.46), respectively, which were both less than 1. Therefore, peramivir 300 mg and 600 mg are both expected to be effective against influenza B virus infections.

PMDA considers as follows:
The NA inhibitory activities (mean IC_{50}) of peramivir for the clinical isolates of influenza B virus from the Japanese phase II and multiregional phase III studies were2.81 and 3.51 (nmol/L), respectively. The two values were comparable and not substantially different from those for strains of other subtypes (except for some strains of viruses with an amino acid substitution, e.g., H275Y mutant virus) [see 3.(i).B.(1) NA inhibitory activity for clinical isolates from clinical studies]. Taking account of this finding in addition to the above explanation by the applicant, the efficacy of peramivir against influenza B virus infections is expected. However, because the number of subjects with influenza B virus infection enrolled into clinical studies was relatively small, it is necessary to collect post-marketing information on the efficacy of peramivir against influenza B virus infections.

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

4.(iii).B.(1).3) Efficacy by time from symptom onset to treatment
PMDA asked the applicant to explain differences in the efficacy of peramivir according to time from onset of influenza symptoms to treatment (i.e., study enrollment).

The applicant responded as follows:
Regarding the time to alleviation of symptoms by time from onset of influenza symptoms to treatment in the Japanese phase II and multiregional phase III studies, the interaction effect between time from symptom onset to treatment and treatment group was tested using Cox proportional hazards model. In both the Japanese phase II and multiregional phase III studies, there was no statistically significant interaction effect between time from symptom onset to treatment and treatment group on the time to alleviation of symptoms (P = 0.2550 and 0.6325,

respectively) and the time from onset of symptoms to treatment had no impact on treatment effectiveness (see the table below).

Time to alleviation of symptoms by time from onset of influenza symptoms to treatment (ITTI)

		Japanese phase II study				Multiregional phase III study			
Time from symptom onset to treatment		Peramivir 300 mg	Peramivir 600 mg	Placebo	*P*-value [a)]	Peramivir 300 mg	Peramivir 600 mg	Oseltamivir phosphate	*P*-value [b)]
0-12 hours	N	17	10	8	0.2550	33	24	30	0.6325
	Median (hours)	65.5	58.7	57.3		53.3	90.3	78.2	
	Median difference (hours)	8.2	1.4			-24.9	12.1		
	Hazard ratio	1.215	1.014			1.126	1.367		
12-24 hours	N	42	41	40		129	117	131	
	Median (hours)	50.9	54.4	93.7		73.8	89.9	88.8	
	Median difference (hours)	-42.8	-39.3			-15.1	1.0		
	Hazard ratio	0.535	0.575			0.930	1.058		
24-36 hours	N	22	31	30		94	114	107	
	Median (hours)	82.5	64.7	91.3		82.6	82.0	80.4	
	Median difference (hours)	-8.8	-26.6			2.2	1.6		
	Hazard ratio	0.979	0.679			0.965	0.980		
36-48 hours	N	18	15	22		108	106	95	
	Median (hours)	55.2	68.1	67.3		81.8	69.4	87.6	
	Median difference (hours)	-12.1	0.8			-5.8	-18.2		
	Hazard ratio	0.420	0.724			0.899	0.767		
> 48 hours	N	-	-	-		-	1	2	
	Median (hours)	-	-	-		-	22.8	57.2	
	Median difference (hours)	-	-			-	-34.4		
	Hazard ratio	-	-			-	0.448		

a) The *P*-value in the Japanese phase II study is the result of a test of interaction effect in Cox proportional hazards model including treatment group, baseline symptom score, current smoking status, time from onset of influenza symptoms to treatment, and treatment group-by-time from onset of influenza symptoms to treatment interaction as explanatory variables.

b) The *P*-value in the multiregional phase III study is the result of a test of interaction effect in Cox proportional hazards model including treatment group, baseline symptom score, current smoking status, country, viral type, time from onset of influenza symptoms to treatment, and treatment group-by-time from onset of influenza symptoms interaction as explanatory variables.

As the time from symptom onset to treatment was > 48 hours in only 1 subject, it was difficult to show the efficacy of peramivir based on the clinical study data. When treatment was initiated within 12 hours of onset of symptoms, the median time to alleviation of symptoms was longer in the peramivir group compared to the control group, except for the peramivir 300 mg group of the multiregional phase III study. This was possibly due to the small number of subjects treated within 12 hours of onset of symptoms.

The above results indicate that there are no differences in the efficacy of peramivir according to the time from symptom onset to treatment and at least the efficacy of peramivir administered within 48 hours of onset of symptoms can be assured.

PMDA considers as follows:

When treatment was initiated within 12 hours of onset of symptoms, the median time to alleviation of symptoms was longer in the peramivir group than in the control group, except for the peramivir 300 mg group of the multiregional phase III study. It is unknown whether this was due only to the small number of subjects treated within 12 hours of onset of symptoms. However, in view of the mechanism of action of peramivir, peramivir is expected to inhibit viral replication even when initiated at earlier timepoints after the onset of symptoms.

From a comprehensive perspective, PMDA accepted the applicant's explanation that the efficacy of peramivir administered within 48 hours of onset of influenza symptoms is assured.

4.(iii).B.(1).4) Efficacy in high-risk patients

The applicant explained the efficacy of peramivir in high-risk patients with influenza virus infection as follows:

The results from clinical studies conducted for the development of oseltamivir phosphate indicate that the time to alleviation of symptoms is longer in high-risk patients (e.g., elderly patients aged ≥ 65 years, patients with heart disease or respiratory disease) than in patients with seasonal influenza virus infection (see the table below).

The results from the main clinical studies of oseltamivir phosphate

Study Number	Study population	Median time to alleviation of symptoms (hours)	
		Oseltamivir phosphate	Placebo
JV15823	Seasonal influenza virus infection	70.0 (N = 121)	93.3 (N = 130)
WV15670		87.4 (N = 157)	116.5 (N = 161)
WV15671		71.5 (N =121)	103.3 (N = 128)
WV15819	Elderly patients aged ≥ 65 years*	161.8 (N = 52)	213.2 (N = 69)
WV15812	Heart disease or respiratory disease*	170.6 (N = 97)	161.0 (N = 104)

* High-risk patients with seasonal influenza virus infection

The median time to alleviation of symptoms in the peramivir groups combined in a Japanese phase III study was 68.6 hours (90% CI, 41.5, 113.4), which was shorter than those in the multiregional phase III study (Peramivir 300 mg group, 78.0 hours [95% CI, 68.4, 88.6]; Peramivir 600 mg group, 81.0 hours [95% CI, 72.7, 91.5]). Thus, the efficacy of peramivir in high-risk patients has been demonstrated. As to efficacy by dose, the median time to alleviation of symptoms (90% CI) in the Japanese phase III study was 114.4 hours (40.2, 235.3) for the peramivir 300 mg group and 42.3 hours (30.0, 82.7) for the peramivir 600 mg group, suggesting

that peramivir 600 mg can improve influenza symptoms faster. As to the number of doses received, since the median time to alleviation of symptoms (90% CI) in the peramivir groups combined was 92.0 hours (14.6, 235.3) in single-dosed patients and 43.2 hours (40.2, 103.3) in multiple-dosed patients (2-day treatment), multiple dose administration is expected to further reduce the time to alleviation of symptoms and treat the illness reliably.

PMDA asked the applicant to explain whether the imbalance in subject background factors between the peramivir 300 mg and 600 mg groups affected the between-group difference in the time to alleviation of symptoms.

The applicant explained as follows:
The imbalance in subject background factors between the groups was assessed.[40] As a result, the factors that were statistically imbalanced between the groups at 0.15 level of significance were smoking history (P = 0.1006, Wilcoxon rank sum test), rapid influenza diagnostic test (rapid antigen test [RAT]) result (P = 0.1047, Fisher's exact test), and influenza viral type (P = 0.0593, Fisher's exact test). However, regarding smoking history, as there was no imbalance in current smoking status (P = 1.0000, Fisher's exact test), it was considered that there was no imbalance between the groups with respect to smoking status. The time to alleviation of symptoms by influenza viral type was as shown in the following table.

Time to alleviation of symptoms by influenza viral type (PPS)

			Combined N = 37	Peramivir 300 mg N = 18	Peramivir 600 mg N = 19
Influenza viral type	A	N	30	12	18
		Median (hours)	42.7	87.7	42.2
		90% CI	30.1, 99.4	30.1, 123.1	26.9, 82.7
	B	N	3	3	-
		Median (hours)	113.4	113.4	-
		90% CI	14.4, 235.3	14.4, 235.3	-
Overall		N	37	18	19
		Median (hours)	68.6	114.4	42.3
		90% CI	41.5, 113.4	40.2, 235.3	30.0, 82.7

Note) Four patients infected with influenza of unknown type (3 patients in the 300 mg group, 1 patient in the 600 mg group) were not assessed for analysis by viral type.

Among patients with influenza A virus infection, the median time to alleviation of symptoms was shorter in the peramivir 600 mg group compared to the peramivir 300 mg group, showing a similar trend to the overall results. Only 3 patients enrolled into the peramivir 300 mg group had influenza B virus infection and the median time to alleviation of symptoms (90% CI) in these

[40] The background factors assessed include gender, age, Body Mass Index (BMI), current smoking status, smoking history, inpatient or outpatient status, poorly controlled diabetes, chronic respiratory disease requiring pharmacotherapy, currently on immunosuppressant medication, time from onset of influenza symptoms to treatment, influenza vaccination status, total score of influenza symptoms (at enrollment), rapid influenza diagnostic test (RAT) result, influenza viral type, and body temperature.

patients was 113.4 hours (14.4, 235.3). Namely, patients with influenza B virus infection were included in the peramivir 300 mg group only, which may have caused a large between-group difference in the time to alleviation of symptoms. No other imbalances in subject demographic factors were identified as widening the between-group difference in the time to alleviation of symptoms. Therefore, it is considered that the imbalance in subject demographic factors between the groups had a small impact on the between-group difference in the time to alleviation of symptoms.

PMDA considers as follows:
Also among patients with influenza A virus infection, the median times to alleviation of symptoms in the peramivir 300 mg and 600 mg groups were 87.7 hours and 42.2 hours, respectively, and the between-group difference was great. Therefore, besides the enrollment of patients with influenza B virus infection into the peramivir 300 mg group only, some other factors contributing to the large between-group difference in the time to alleviation of symptoms may have existed, but the assessment of subject demographic factors identified no other factors. The applicant's explanation that the impact of the imbalance in subject demographic factors between the groups on the between-group difference in the time to alleviation of symptoms was small is acceptable.

The difference in the time to alleviation of symptoms between single-dosed and multiple-dosed (at least 2 doses) patients was great (92.0 hours and 64.1 hours, respectively). The criteria for continuing treatment from Day 2 onward were as follows: "If body temperature is ≥ 37.5°C, treatment should be continued. If body temperature is < 37.5°C, treatment should be stopped as a rule. However, if treatment continuation is judged necessary by the investigator (or sub-investigator) based on clinical symptoms, treatment may be continued." PMDA asked the applicant to explain whether treatment continuation (discontinuation) from Day 2 onward had been decided appropriately for single-dosed and multiple-dosed patients.

The applicant responded as follows:
Body temperature was ≥ 37.5°C on the morning of Day 2[41] in 0% (0 of 10 patients) of single-dosed patients and 63% (17 of 27 patients) of multiple-dosed patients. There were no single-dosed patients who met the criteria for treatment continuation, but did not continue treatment. Also, treatment continuation was appropriately decided for 10 multiple-dosed patients with body temperature < 37.5°C on the morning of Day 2, as most of these patients had

[41] The protocol required that from Day 2 onward, whether to continue treatment should be decided and the drug should be administered in the morning as a rule.

persistent influenza symptoms (see the table below).

Reasons for treatment continuation in 10 multiple-dosed patients with body temperature < 37.5°C on the morning of Day 2

Subject Number	Body temperature on the morning of Day 2 (°C)	Influenza symptom score		Reason for treatment continuation
		Baseline	Morning of Day 2	
1	36.7	11	5	Treatment was continued because body temperature was 37.6°C on clinical examination.
2	35.8	5	1	To prevent worsening of the patient's symptoms as the patient had a fever of ≥ 37.5°C on the previous night.
3	36.6	15	12	Body temperature was 36.6°C, but treatment continuation was judged necessary, taking account of influenza symptoms etc.
4	36.1	15	10	Persistent influenza symptoms
5	36.9	14	5	Body temperature was 36.9°C, but treatment continuation was judged necessary due to persistent influenza-like symptoms.
6	37.3	7	2	Body temperature was ≥ 37.5°C.* *Treatment continuation was decided based on body temperature at noon of Day 2 (37.6°C).
7	37.3	10	8	Severe general malaise
8	37.0	15	11	Body temperature was 37.0°C, but treatment continuation was judged necessary because the influence of corticosteroids was also suspected and influenza-like symptoms were persistent.
9	37.0	12	5	Persistent influenza symptoms
10	36.5	11	10	It was likely that fever was alleviated by a concomitant medication. Influenza symptoms were persistent.

The mean body temperature and the mean total score of influenza symptoms[42] on the morning of Day 2 were 37.50°C and 9.8, respectively, in multiple-dosed patients, which were higher than 36.75°C and 7.2, respectively, in single-dosed patients, and patients with relatively severe, persistent symptoms received multiple doses. Therefore, multiple dose administration was decided in accordance with the protocol and there were no differences in the way to decide whether to continue treatment between single-dosed and multiple-dosed patients.

The reasons for treatment continuation in patients who continued treatment from Day 3 onward were as shown below.

[42] Total score of 7 symptoms of influenza (cough, sore throat, headache, nasal congestion, feverishness or chills, myalgia or arthralgia, fatigue). Scores were calculated according to the severity of each symptom on a four-point scale (absent, 0; mild, 1; moderate, 2; severe, 3).

Body temperature, influenza symptom score, and reason for treatment continuation in patients treated for ≥ 3 days

3-day treatment				
Subject Number	Body temperature on the morning of Day 3 (°C)	Influenza symptom score		Reason for treatment continuation
		Baseline	Morning of Day 3	
11	36.6	9	4	Because the subject complained of malaise and was unlikely to recover from influenza, treatment was continued.
12	37.5	12	13	Body temperature ≥ 37.5°C
4-day treatment				
Subject Number	Body temperature on the morning of Day 4 (°C)	Influenza symptom score		Reason for treatment continuation
		Baseline	Morning of Day 4	
13	37.1	12	10	Influenza symptoms of cough, malaise, and chills were persistent.
5-day treatment				
Subject Number	Body temperature on the morning of Day 5 (°C)	Influenza symptom score		Reason for treatment continuation
		Baseline	Morning of Day 5	
14	37.1	11	8	Persistent influenza symptoms

Based on the above explanation by the applicant, PMDA concluded that there were largely no problems with the decisions to continue treatment, which were not relevant to the large difference in the time to alleviation of symptoms between single-dosed and multiple-dosed patients. However, PMDA considers that it is doubtful whether the decision to continue treatment was appropriate for Subject Number 2 in the above table, because the subject's body temperature did not reach ≥ 37.5°C and the influenza symptom score was as low as 1 (mild fatigue) on the morning of Day 2. In addition, the investigator decided to continue treatment from Day 2 onward in order to prevent worsening of symptoms. Therefore, PMDA considers that physicians should be advised to carefully determine the need to continue treatment from Day 2 onward. After Subject Number 2 in the above table was excluded from the PPS, the efficacy data from 36 patients were reanalyzed, which did not significantly affect the efficacy evaluation of peramivir in high-risk patients.[43]

Then, as to the number of doses received by patients in the peramivir groups combined, when single-dosed patients were compared to multiple-dosed patients, differences in the distribution of patients between the doses may have contributed to the large difference in the time to alleviation of symptoms between single-dosed and multiple-dosed patients (see the table below). Meanwhile, in the Japanese phase III study, the limited number of patients were investigated, which made it difficult to discuss comparability stringently. Also, body temperature and the

[43] The median time to alleviation of symptoms (90% CI) was 114.4 hours (40.2, 235.3) in the peramivir 300 mg group and 42.7 hours (30.0, 99.4) in the peramivir 600 mg group. The median time to alleviation of symptoms (90% CI) in the peramivir groups combined by the number of doses received was 92.0 hours (14.6, 235.3) in single-dosed patients and 53.6 hours (41.5, 103.3) in patients treated for 2 days.

total score of influenza symptoms were higher in multiple-dosed patients than in single-dosed patients and more multiple-dosed patients had severe symptoms. Taking account of these findings, PMDA considers that the applicant's claim that as long as there is no safety concern, a higher dose (peramivir 600 mg) and a greater number of doses (multiple dose administration) are expected to be more effective in high-risk patients, is understandable.

Time to alleviation of symptoms by duration of treatment (PPS)

Duration of treatment		Combined N = 37	Peramivir 300 mg N = 18	Peramivir 600 mg N = 19
1 day	N	10	7	3
	Median (hours)	92.0	132.0	14.6
	90% CI	14.6, 235.3	23.2, +infinity	13.2, 68.6
≥ 2 days	N	27	11	16
	Median (hours)	64.1	111.2	42.7
	90% CI	41.5, 111.2	40.2, 123.1	30.0, 103.3

Based on the above, PMDA considers as follows:

The results of the Japanese phase III study indicate that the efficacy of peramivir is expected also in high-risk patients and that the time to alleviation of symptoms tends to be shorter following multiple dose administration of peramivir 600 mg compared with 300 mg.

4.(iii).B.(1).5) Resistance to peramivir

In a Japanese phase II study, there was a ≥ 3-fold increase in the NA IC_{50} of peramivir between screening and post-dose in 5 subjects. PMDA asked the applicant to explain these 5 subjects.

The applicant responded as follows:

In the peramivir 600 mg group of the Japanese phase II study, there was a ≥ 3-fold increase in the IC_{50} of peramivir between screening and post-dose in 5 subjects and all of the final isolates from these 5 subjects contained the H275Y mutation. Viral type/subtype, virus titer, and NA inhibitory activity over time and the time to alleviation of symptoms in these 5 subjects were as shown in the following table.

Subjects with higher NA inhibitory activity (IC_{50}) ratio in Japanese phase II study

Viral type/subtype	Date	Virus titer [log_{10} ($TCID_{50}$/mL)][a)]	IC_{50} (nM)	IC_{50} (ng/mL)	Ratio of IC_{50}	Time to alleviation of symptoms (hours)
A/H1	20[redacted]	4.4	0.966	0.32	-	54.4
	20[redacted]	3.8	-	-	-	
	20[redacted]	2.8	-	-	-	
	20[redacted]	3.1	14.50	4.76	15.01	
	20[redacted]	1.1	-	-	-	
A/-	20[redacted]	2.1	1.720	0.56	-	29.9
	20[redacted]	1.1	-	-	-	
	20[redacted]	2.4	31.50	10.34	18.314	
	20[redacted]	1.1	-	-	-	
A/H1	20[redacted]	4.1	1.350	0.44	-	45.0
	20[redacted]	2.1	-	-	-	
	20[redacted]	2.1	-	-	-	
	20[redacted]	1.4	27.60	9.06	20.444	
	20[redacted]	1.1	-	-	-	
A/H1	20[redacted]	5.4	1.120	0.37	-	174.1
	20[redacted]	2.8	-	-	-	
	20[redacted]	1.4	-	-	-	
	20[redacted]	1.1	27.80	9.13	24.821	
	20[redacted]	1.1	-	-	-	
A/H1	20[redacted]	5.4	1.470	0.48	-	140.1
	20[redacted]	2.4	-	-	-	
	20[redacted]	2.8	-	-	-	
	20[redacted]	4.1	-	-	-	
	20[redacted]	1.1	30.30	9.95	20.612	

a) [log_{10} ($TCID_{50}$ / mL)] below the detection limit is expressed as 1.1.

The possible cause for a ≥ 3-fold increase in the IC_{50} after peramivir administration in the 5 subjects was that a trace amount of the H275Y mutant virus was already present in the wild-type virus population at screening. Namely, because peramivir has a weaker inhibitory activity against the H275Y mutant virus compared to the wild-type virus, peramivir potently inhibited the replication of the wild-type virus relative to the mutant virus and their relative abundance was reversed due to selective pressure by peramivir and the portion of the H275Y mutant virus became apparent, resulting in increases in the NA IC_{50} values of peramivir for the final isolates.

In all of the 5 subjects, the virus titer fell below the detection limit by Visit 5 (Day 9) and the time to alleviation of symptoms varied, ranging from 29.9 to 174.1 hours. Therefore, there was no consistent trend towards a longer time to alleviation of symptoms in patients with higher IC_{50} values.

PMDA considers as follows:

The applicant discussed that the IC_{50} increased ≥ 3-fold after peramivir administration possibly because the H275Y mutant virus that was present in trace amount from the beginning of infection became apparent due to selective pressure by peramivir. This inference is understandable, given that the virus titer in each subject was reduced from screening. In this regard, the applicant's explanation is acceptable. Moreover, analysis of these subjects suggested

no specific trend towards a longer time to alleviation of symptoms in patients with higher IC_{50} values. However, as the number of subjects analyzed was limited (5 subjects) and there was also a large variability in the time to alleviation of symptoms, it is difficult to reach a definitive conclusion on the effect of higher IC_{50} values after peramivir administration on the clinical course.

4.(iii).B.(2) Safety

PMDA's review mainly focused on the following points for safety evaluation of peramivir.

4.(iii).B.(2).1) Dose and safety of peramivir

The applicant explained the dose and safety of peramivir as follows:

The incidences of adverse events and adverse drug reactions by dose of peramivir were as shown in the following table.

Incidences of adverse events and adverse drug reactions by dose and study

	Adverse event			Adverse drug reaction		
Japanese phase II study						
	Peramivir 300 mg	Peramivir 600 mg	Placebo	Peramivir 300 mg	Peramivir 600 mg	Placebo
No. of subjects evaluated	99	99	100	99	99	100
No. of subjects with event (incidence)	87 (87.9%)	90 (90.9%)	91 (91.0%)	52 (52.5%)	56 (56.6%)	51 (51.0%)
95% CI (%)	79.8, 93.6	83.4, 95.8	83.6, 95.8	42.2, 62.7	46.2, 66.5	40.8, 61.1
P-value (vs. placebo)	0.4986	1.0000	-	0.8875	0.4782	-
Multiregional phase III study						
	Peramivir 300 mg	Peramivir 600 mg	Oseltamivir phosphate	Peramivir 300 mg	Peramivir 600 mg	Oseltamivir phosphate
No. of subjects evaluated	364	364	365	364	364	365
No. of subjects with event (incidence)	170 (46.7%)	174 (47.8%)	178 (48.8%)	51 (14.0%)	66 (18.1%)	73 (20.0%)
95% CI (%)	41.5,52.0	42.6, 53.1	43.5, 54.0	10.6, 18.0	14.3, 22.5	16.0, 24.5
P-value (vs. oseltamivir phosphate)	0.6040	0.8242	-	0.0382*	0.5718	-
Japanese phase III study						
	Peramivir 300 mg	Peramivir 600 mg	-	Peramivir 300 mg	Peramivir 600 mg	-
No. of subjects evaluated	21	21	-	21	21	-
No. of subjects with event (incidence)	15 (71.4%)	16 (76.2%)	-	6 (28.6%)	8 (38.1%)	-
95% CI (%)	47.8, 88.7	52.8, 91.8	-	11.3, 52.2	18.1, 61.6	-
P-value (vs. peramivir 300 mg)	-	1.0000	-	-	0.7442	-

Analysis method: Fisher's exact test
*: *P*-value < 0.05

When pooled analysis of 2 studies, Japanese phase II and multiregional phase III studies, was performed to compare the incidences of individual adverse events and adverse drug reactions, there were no events with a markedly higher incidence in the peramivir 600 mg group than in the peramivir 300 mg group (see the table below).

Adverse events by dose (reported by at least 2.5% of subjects in either group)

	Adverse event		Adverse drug reaction	
	Peramivir 300 mg N = 463	Peramivir 600 mg N = 463	Peramivir 300 mg N = 463	Peramivir 600 mg N = 463
Gastrointestinal disorders				
Diarrhoea	38 (39) 8.2%	45 (47) 9.7%	25 (26) 5.4%	30 (31) 6.5%
Nausea	11 (11) 2.4%	14 (14) 3.0%	4 (4) 0.9%	11 (11) 2.4%
Investigations				
Neutrophil count decreased	39 (39) 8.4%	39 (39) 8.4%	9 (9) 1.9%	15 (15) 3.2%
Blood glucose increased	29 (29) 6.3%	31 (31) 6.7%	7 (7) 1.5%	4 (4) 0.9%
Protein urine present	26 (26) 5.6%	27 (27) 5.8%	13 (13) 2.8%	11 (11) 2.4%
White blood cells urine positive	22 (22) 4.8%	17 (17) 3.7%	3 (3) 0.6%	7 (7) 1.5%
Monocyte percentage increased	20 (20) 4.3%	18 (18) 3.9%	0 (0) 0.0%	0 (0) 0.0%
ALT increased	14 (14) 3.0%	17 (17) 3.7%	7 (7) 1.5%	13 (13) 2.8%
Lymphocyte percentage increased	14 (14) 3.0%	14 (14) 3.0%	6 (6) 1.3%	5 (5) 1.1%
White blood cell count decreased	12 (12) 2.6%	13 (13) 2.8%	7 (7) 1.5%	8 (8) 1.7%
Urine β2-MG increased	14 (14) 3.0%	8 (8) 1.7%	12 (12) 2.6%	7 (7) 1.5%
Blood phosphorus decreased	13 (13) 2.8%	7 (7) 1.5%	6 (6) 1.3%	1 (1) 0.2%
AST increased	4 (4) 0.9%	13 (13) 2.8%	3 (3) 0.6%	12 (12) 2.6%

No. of subjects with event (No. of events) Incidence %

PMDA considers as follows:

Although the incidences of adverse events and adverse drug reactions tended to be higher in the peramivir 600 mg group than in the peramivir 300 mg group, since (a) the Japanese phase II study showed no significant differences in the incidence of adverse events or adverse drug reactions between peramivir 300 mg or 600 mg and placebo and (b) the incidence of adverse events or adverse drug reactions was not higher in the peramivir group compared with the oseltamivir phosphate group in the multiregional phase III study, there should be no particular problems with increasing dose. On the other hand, when the incidences of individual events were compared, the incidences of diarrhoea, nausea, ALT increased, white blood cell count decreased, and AST increased, both as adverse events and as adverse drug reactions, tended to be higher in the peramivir 600 mg group than in the peramivir 300 mg group. Therefore, the possible occurrence of these events should be kept in mind.

4.(iii).B.(2).2) Safety of multiple-dose peramivir

In a Japanese phase III study, peramivir was to be administered as a single dose or multiple doses (for up to 5 days) and 11 subjects received a single dose and 31 subjects received multiple doses (2 doses, 26 subjects; 3 doses, 3 subjects; 4 doses, 1 subject; 5 doses, 1 subject).

The applicant explained the safety of single and multiple doses of peramivir as follows:

The incidences of adverse events and adverse drug reactions were 63.6% (7 of 11 subjects) and

9.1% (1 of 11 subjects), respectively, in single-dosed subjects and 77.4% (24 of 31 subjects) and 41.9% (13 of 31 subjects), respectively, in multiple-dosed subjects.

The following table lists adverse events and adverse drug reactions which occurred at a higher incidence in multiple-dosed subjects than in single-dosed subjects and which were noted in at least 2 multiple-dosed subjects.

Of these events, those occurring in at least 4 multiple-dosed subjects were blood glucose increased, eosinophil count increased, neutrophil count decreased, and blood phosphorus decreased. Blood glucose increased was reported as a severe adverse event by 1 single-dosed subject and by 1 multiple-dosed subject. The event in the 1 multiple-dosed subject was classified as an adverse drug reaction, but was inferred not to be strongly suspected to be related to peramivir, because this subject had poorly controlled diabetes. Among adverse events and adverse drug reactions with a higher incidence in multiple-dosed subjects, there were no events with an outcome of no change or death. One adverse event of eosinophil count increased with an outcome of worsening was reported by 1 multiple-dosed subject, but this subject had concurrent asthma and the adverse event was considered attributable to asthma. The outcomes of other adverse events and adverse drug reactions were reported as improved or resolved.

The above findings indicate that there is no trend towards increasing safety problems with the multiple doses of peramivir.

Adverse events and adverse drug reactions which occurred at a higher incidence in multiple-dosed subjects than in single-dosed subjects and which were noted in at least 2 multiple-dosed subjects

Adverse event	Single dose N = 11	Multiple doses N = 31
Blood glucose increased	2 (18.2%)	8 (25.8%)
Neutrophil count decreased	1 (9.1%)	4 (12.9%)
Eosinophil count increased	0 (0.0%)	4 (12.9%)
Blood phosphorus decreased	0 (0.0%)	4 (12.9%)
Protein total decreased	1 (9.1%)	3 (9.7%)
Pneumonia	0 (0.0%)	3 (9.7%)
Stomatitis	0 (0.0%)	2 (6.5%)
Urine ketone body present	0 (0.0%)	2 (6.5%)
Adverse drug reaction	Single dose N=11	Multiple doses N=31
Blood glucose increased	0 (0.0%)	3 (9.7%)

Number of subjects with event (Incidence, %)

PMDA considers as follows:

Based on the above explanation by the applicant, there has been no specific trend towards an increase in the risk of clinically relevant adverse events caused by multiple doses of peramivir. However, because the number of multiple-dosed subjects in the Japanese phase III study was

small and especially, the number of subjects who received at least 3 doses was 5 (300 mg, 3 subjects; 600 mg, 2 subjects), safety information is limited. Therefore, the need for multiple dose administration of peramivir should be carefully determined based on the patient's symptoms etc. It is necessary to adequately alert medical practices to this point and continue to collect post-marketing information on safety especially in patients who received at least 3 doses of peramivir and differences in the safety profile between single-dosed and multiple-dosed patients.

4.(iii).B.(2).3) Nephrotoxicity

Non-clinical studies, i.e. single intravenous and 1-week intravenous toxicity studies in rabbits suggested the nephrotoxicity of peramivir [see 3.(iii).A.(7).3) Nephrotoxicity studies in rabbits]. Thus, in a Japanese phase II study, NAG, α1-MG, β2-MG, and urinary albumin were monitored to evaluate the nephrotoxicity of peramivir in humans. As a result, the incidences of relevant adverse events are as shown in the following table.

Incidences of adverse events and adverse drug reactions of NAG, α1-MG, β2-MG, and urinary albumin in Japanese phase II study

	Peramivir 300 mg N = 99	Peramivir 600 mg N = 99	Peramivir combined N = 198	Placebo N = 100
Adverse event				
Urine β2 MG increased	14 (14.1%)	8 (8.1%)	22 (11.1%)	11 (11.0%)
β-NAG increased	9 (9.1%)	5 (5.1%)	14 (7.1%)	5 (5.0%)
Urine α1 MG increased	6 (6.1%)	6 (6.1%)	12 (6.1%)	6 (6.0%)
Albumin urine present	5 (5.1%)	5 (5.1%)	10 (5.1%)	6 (6.0%)
Adverse drug reaction				
Urine β2 MG increased	12 (12.1%)	7 (7.1%)	19 (9.6%)	10 (10.0%)
β-NAG increased	7 (7.1%)	5 (5.1%)	12 (6.1%)	5 (5.0%)
Urine α1 MG increased	5 (5.1%)	6 (6.1%)	11 (5.6%)	6 (6.0%)
Albumin urine present	5 (5.1%)	5 (5.1%)	10 (5.1%)	5 (5.0%)

Number of subjects with event (Incidence %)

The applicant explained the laboratory test results for NAG, α1-MG, β2-MG, and urinary albumin as follows:

With respect to the time courses of laboratory values after study drug administration, NAG was elevated on Day 3 in the peramivir group, but a similar course was seen in the placebo group as well. The time courses of other parameters were also similar between the peramivir and placebo groups (see the table below). Thus, there should be no particular concern about the nephrotoxicity of peramivir in humans.

Time courses of NAG, α1-MG, β2-MG, and urinary albumin in Japanese phase II study

	Timepoint	Peramivir			Placebo		
		N	Mean	SD	N	Mean	SD
NAG (U/L)	Baseline	197	4.30	4.34	100	4.89	4.55
	Day 3	195	6.76	5.41	100	7.67	6.50
	End of study	192	4.33	3.91	99	4.79	3.48
α1-MG (mg/L)	Baseline	197	10.304	10.467	100	13.985	18.117
	Day 3	195	9.851	9.887	100	13.802	16.375
	End of study	192	3.818	3.894	99	4.713	5.411
β2-MG (μg/L)	Baseline	197	2126.8	4194.0	100	5270.6	21949.6
	Day 3	195	686.0	1389.4	100	2270.1	10015.7
	End of study	192	114.3	156.4	99	174.0	370.4
Urinary albumin (mg/g.Cr)	Baseline	197	18.89	75.85	100	15.91	29.15
	Day 3	195	13.95	33.99	100	20.86	50.17
	End of study	192	9.87	34.57	99	8.04	14.22

PMDA considers as follows:

In the Japanese phase II study, the incidences of adverse events and adverse drug reactions of NAG, α1-MG, β2-MG, and urinary albumin were not evidently higher in the peramivir group than in the placebo group. Also, the time courses of NAG, α1-MG, and β2-MG after administration were similar between the peramivir and placebo groups and urinary albumin was elevated on Day 3 in the placebo group, but there was no increase after administration in the peramivir group, suggesting no nephrotoxicity of peramivir.

Therefore, PMDA concluded that although the nephrotoxicity studies in rabbits suggested the nephrotoxicity of peramivir, the risk of nephrotoxicity in humans has not been suggested in the above clinical study.

4.(iii).B.(2).4) QTc interval prolongation

QTc interval prolongation was reported as a severe adverse event in 16 subjects in the peramivir group and as a severe adverse drug reaction in 1 subject who received a single dose in the peramivir 300 mg group and 1 subject who received a single dose in the peramivir 600 mg group in Japanese phase II, multiregional phase III, and Japanese phase III studies. The applicant explained the potential of peramivir to cause QTc interval prolongation as follows.

Cardiovascular adverse drug reactions such as QTc interval prolongation were reported in a foreign phase I study (Study BCX1812-104). Therefore, in order to watch for the cardiovascular effects of peramivir, using the ECG data from the Japanese phase II, multiregional phase III, and Japanese phase III studies, a QTc interval increase from baseline ≥ 60 msec or a QTc interval ≥ 480 msec was identified as an adverse event and was graded as “severe” according to

the DAIDS AE grading table.[44] The incidence of an adverse event of QTc interval prolongation in the peramivir groups from the Japanese phase II and multiregional phase III studies, which were controlled studies, was 1.7% (16 of 926 subjects) and the incidences of an adverse event and an adverse drug reaction of QTc interval prolongation by treatment group in each study were as shown in the following table.

Incidences of adverse event and adverse drug reaction of QTc interval prolongation

Japanese phase II study				Multiregional phase III study				Peramivir groups combined	
Adverse event		Adverse drug reaction		Adverse event		Adverse drug reaction			
Peramivir N = 198	Placebo N = 100	Peramivir N = 198	Placebo N = 100	Peramivir N = 728	Oseltamivir phosphate N = 365	Peramivir N = 728	Oseltamivir phosphate N = 365	Adverse event N = 926	Adverse drug reaction N = 926
3 (3) 1.5%	3 (3) 3.0%	1 (1) 0.5%	0 (0) 0.0%	13 (13) 1.8%	10 (10) 2.7%	1 (1) 0.1%	0 (0) 0.0%	16 (16) 1.7%	2 (2) 0.2%

No. of subjects with event (No. of events)
Incidence, %

Although 1 adverse drug reaction of QTc interval prolongation each occurred in the Japanese phase II and multiregional phase III studies, both developed on or after Day 3 and a causal relationship to peramivir is not strongly suspected. Since the results of a foreign thorough QT/QTc study of single doses of 600 mg and 1200 mg of peramivir vs. MFLX and placebo controls (Study BCX1812-106) were negative, peramivir is unlikely to cause serious arrhythmia such as torsade de pointes and the cardiovascular effects of peramivir should be insignificant.

PMDA concluded that because there were no major differences in the incidence of QTc interval prolongation between the peramivir and placebo groups and the results of the foreign thorough QT/QTc study (Study BCX1812-106) were negative, there is no particular concern about an increased risk of QTc interval prolongation in association with the use of peramivir.

4.(iii).B.(2).5) Ethnic differences

PMDA asked the applicant to explain differences in the profile of adverse events and adverse drug reactions by comparing the safety data from the multiregional phase III study between the Japanese subpopuration and the Korean and Taiwanese subpopulations.

The applicant responded as follows:

The incidence of adverse events by country (region) was 48.6% (241 of 496 subjects) in Japan, 45.7% (32 of 70 subjects) in Korea, and 43.8% (71 of 162 subjects) in Taiwan. The incidence of

[44] Division of Aids table for Grading the Severity of Adult and Pediatric Adverse Events Publish Data, 2004;1:1-20.

adverse drug reactions by country (region) was 18.3% (91 of 496 subjects) in Japan, 14.3% (10 of 70 subjects) in Korea, and 9.9% (16 of 162 subjects) in Taiwan. Events reported by at least 2.5% of subjects in any country (region) are as shown in the following table. When individual events were compared, events occurring more frequently in Japanese subjects than in Korean and Taiwanese subjects were diarrhoea, neutrophil count decreased, protein urine present, and ALT increased.

Incidences of adverse events and adverse drug reactions by country (region) in peramivir group in multiregional phase III study

	Adverse event				Adverse drug reaction			
	Japan	S. Korea	Taiwan	Overall	Japan	S. Korea	Taiwan	Overall
No. of subjects evaluated	496	70	162	728	496	70	162	728
No. of subjects with event	241	32	71	344	91	10	16	117
Incidence	48.6%	45.7%	43.8%	47.3%	18.3%	14.3%	9.9%	16.1%
Gastrointestinal disorders								
Diarrhoea	46 (9.3%)	3 (4.3%)	5 (3.1%)	54 (7.4%)	29 (5.8%)	3 (4.3%)	2 (1.2%)	34 (4.7%)
Nausea	12 (2.4%)	4 (5.7%)	0 (0.0%)	16 (2.2%)	6 (1.2%)	3 (4.3%)	0 (0.0%)	9 (1.2%)
Infections and infestations								
Bronchitis	4 (0.8%)	0 (0.0%)	8 (4.9%)	12 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations								
Neutrophil count decreased	59 (11.9%)	8 (11.4%)	10 (6.2%)	77 (10.6%)	21 (4.2%)	1 (1.4%)	1 (0.6%)	23 (3.2%)
Protein urine present	26 (5.2%)	2 (2.9%)	5 (3.1%)	33 (4.5%)	8 (1.6%)	1 (1.4%)	2 (1.2%)	11 (1.5%)
Blood glucose increased	18 (3.6%)	4 (5.7%)	3 (1.9%)	25 (3.4%)	1 (0.2%)	1 (1.4%)	0 (0.0%)	2 (0.3%)
White blood cells urine positive	13 (2.6%)	4 (5.7%)	5 (3.1%)	22 (3.0%)	4 (0.8%)	1 (1.4%)	1 (0.6%)	6 (0.8%)
ALT increased	18 (3.6%)	0 (0.0%)	2 (1.2%)	20 (2.7%)	11 (2.2%)	0 (0.0%)	0 (0.0%)	11 (1.5%)
Blood phosphorus decreased	10 (2.0%)	3 (4.3%)	1 (0.6%)	14 (1.9%)	2 (0.4%)	1 (1.4%)	0 (0.0%)	3 (0.4%)
Electrocardiogram QT prolonged	8 (1.6%)	1 (1.4%)	4 (2.5%)	13 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.1%)
Red blood cells urine positive	8 (1.6%)	1 (1.4%)	4 (2.5%)	13 (1.8%)	4 (0.8%)	0 (0.0%)	1 (0.6%)	5 (0.7%)
Blood urine present	5 (1.0%)	2 (2.9%)	5 (3.1%)	12 (1.6%)	2 (0.4%)	0 (0.0%)	1 (0.6%)	3 (0.4%)
Metabolism and nutrition disorders								
Anorexia	1 (0.2%)	4 (5.7%)	0 (0.0%)	5 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders								
Dizziness	3 (0.6%)	1 (1.4%)	6 (3.7%)	10 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.1%)
Psychiatric disorders								
Insomnia	0 (0.0%)	3 (4.3%)	2 (1.2%)	5 (0.7%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	2 (0.3%)

Number of subjects with event (Incidence %)

PMDA considers that it is necessary to note that adverse events of diarrhoea, neutrophil count decreased, protein urine present, and ALT increased occurred more frequently in the Japanese subpopulation compared with the Korean and Taiwanese subpopulations. As to the incidences of these events in the Japanese subpopulation, the incidence of ALT increased tended to be slightly higher in the peramivir group, while there were no major differences in the incidences of other events between the peramivir and oseltamivir phosphate groups. Therefore, PMDA concluded that these events will not become a clinically relevant problem (see the table below).

Incidences of adverse events and adverse drug reactions of diarrhoea, neutrophil count decreased, protein urine present, and ALT increased in Japanese subpopulation

	Adverse event			Adverse drug reaction		
	Peramivir 300 mg N = 247	Peramivir 600 mg N = 249	Oseltamivir phosphate N = 246	Peramivir 300 mg N = 247	Peramivir 600 mg N = 249	Oseltamivir phosphate N = 246
Diarrhoea	22 (8.9%)	24 (9.6%)	22 (8.9%)	13 (5.3%)	16 (6.4%)	14 (5.7%)
Neutrophil count decreased	28 (11.3%)	31 (12.4%)	29 (11.8%)	8 (3.2%)	13 (5.2%)	12 (4.9%)
Protein urine present	15 (6.1%)	11 (4.4%)	19 (7.7%)	6 (2.4%)	2 (0.8%)	8 (3.3%)
ALT increased	8 (3.2%)	10 (4.0%)	4 (1.6%)	5 (2.0%)	6 (2.4%)	2 (0.8%)

Number of subjects with event (Incidence %)

4.(iii).B.(2).6) Safety in special populations

(a) Safety in patients with renal impairment

The applicant explained the safety of peramivir in patients with renal impairment as follows:

Adverse events reported in Japanese phase II and multiregional phase III studies were classified according to the degree of renal impairment (CLcr) and events reported by at least 2.5% of patients in any category were examined (see the table below).

Incidences of adverse events and adverse drug reactions by CLcr in Japanese phase II and multiregional phase III studies (events with an incidence ≥ 2.5%)

	Adverse event				Adverse drug reaction			
	CLcr ≥ 80 mL/min	CLcr 50 - 80 mL/min	CLcr < 50 mL/min	Overall	CLcr ≥ 80 mL/min	CLcr 50 - 80 mL/min	CLcr < 50 mL/min	Overall
No. of subjects evaluated	787	132	7	926	787	132	7	926
No. of subjects with event	439	78	4	521	190	33	2	225
Incidence	55.8%	59.1%	57.1%	56.3%	24.1%	25.0%	28.6%	24.3%
Gastrointestinal disorders								
Diarrhoea	74 (9.4%)	8 (6.1%)	1 (14.3%)	83 (9.0%)	49 (6.2%)	5 (3.8%)	1 (14.3%)	55 (5.9%)
Nausea	24 (3.0%)	1 (0.8%)	0 (0.0%)	25 (2.7%)	14 (1.8%)	1 (0.8%)	0 (0.0%)	15 (1.6%)
Investigations								
Neutrophil count decreased	65 (8.3%)	12 (9.1%)	1 (14.3%)	78 (8.4%)	19 (2.4%)	4 (3.0%)	1 (14.3%)	24 (2.6%)
Blood glucose increased	47 (6.0%)	12 (9.1%)	1 (14.3%)	60 (6.5%)	9 (1.1%)	2 (1.5%)	0 (0.0%)	11 (1.2%)
Protein urine present	41 (5.2%)	11 (8.3%)	1 (14.3%)	53 (5.7%)	20 (2.5%)	3 (2.3%)	1 (14.3%)	24 (2.6%)
White blood cells urine positive	29 (3.7%)	9 (6.8%)	1 (14.3%)	39 (4.2%)	8 (1.0%)	2 (1.5%)	0 (0.0%)	10 (1.1%)
Monocyte percentage increased	36 (4.6%)	2 (1.5%)	0 (0.0%)	38 (4.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT increased	27 (3.4%)	4 (3.0%)	0 (0.0%)	31 (3.3%)	18 (2.3%)	2 (1.5%)	0 (0.0%)	20 (2.2%)
Lymphocyte percentage increased	25 (3.2%)	3 (2.3%)	0 (0.0%)	28 (3.0%)	8 (1.0%)	3 (2.3%)	0 (0.0%)	11 (1.2%)
White blood cell count decreased	22 (2.8%)	2 (1.5%)	1 (14.3%)	25 (2.7%)	13 (1.7%)	1 (0.8%)	1 (14.3%)	15 (1.6%)
Urine β2-MG increased	21 (2.7%)	1 (0.8%)	0 (0.0%)	22 (2.4%)	18 (2.3%)	1 (0.8%)	0 (0.0%)	19 (2.1%)
Blood phosphorus decreased	13 (1.7%)	7 (5.3%)	0 (0.0%)	20 (2.2%)	4 (0.5%)	3 (2.3%)	0 (0.0%)	7 (0.8%)
Glucose urine present	12 (1.5%)	5 (3.8%)	0 (0.0%)	17 (1.8%)	4 (0.5%)	1 (0.8%)	0 (0.0%)	5 (0.5%)
Electrocardiogram QT prolonged	11 (1.4%)	4 (3.0%)	1 (14.3%)	16 (1.7%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
LDH increased	5 (0.6%)	4 (3.0%)	0 (0.0%)	9 (1.0%)	5 (0.6%)	4 (3.0%)	0 (0.0%)	9 (1.0%)
Blood urea increased	3 (0.4%)	3 (2.3%)	1 (14.3%)	7 (0.8%)	2 (0.3%)	3 (2.3%)	1 (14.3%)	6 (0.6%)

Number of subjects with event (Incidence, %)

The incidence of adverse events by CLcr was 55.8% (439 of 787 subjects) in patients with normal renal function (CLcr ≥ 80 mL/min), 59.1% (78 of 132 subjects) in patients with mild renal impairment (CLcr 50-80 mL/min), and 57.1% (4 of 7 subjects) in patients with moderate renal impairment (CLcr < 50 mL/min) and the incidence of adverse events was comparable

regardless of the degree of renal impairment. Because the number of patients with moderate renal impairment (CLcr < 50 mL/min) was only 7 subjects, adverse events were compared between patients with normal renal function (CLcr ≥ 80 mL/min) and patients with mild renal impairment (CLcr 50-80 mL/min) requiring no dose adjustment. As a result, none of the events had a particularly higher incidence in patients with mild renal impairment than in patients with normal renal function.

Also, in a foreign phase I study (Study Hi-[redacted]-105) in which a single dose of 2 mg/kg of peramivir was administered to subjects with normal renal function and subjects with mild renal impairment to end-stage renal disease, there were no differences in the incidence of adverse events according to the degree of renal impairment.

PMDA considers that as the number of patients with moderate or severe (CLcr < 50 mL/min) renal impairment studied was limited and the safety of peramivir has not adequately been evaluated, it is necessary to collect post-marketing safety information regarding the use of peramivir in patients with renal impairment.

(b) Safety in elderly

The applicant explained the safety of peramivir in the elderly as follows:

In Japanese phase II and multiregional phase III studies, the incidence of adverse events was 81.3% (13 of 16 subjects) in subjects ≥ 65 years of age and 55.8% (508 of 910 subjects) in subjects < 65 years of age and the incidence of adverse drug reactions was 18.8% (3 of 16 subjects) and 24.4% (222 of 910 subjects), respectively. The incidence of blood glucose increased was higher in subjects ≥ 65 years of age (18.8% [3 of 16 subjects]) than in subjects < 65 years of age (6.3% [57 of 910 subjects]).

PMDA considers as follows:

No trend towards an increase in clinically relevant safety risk in elderly patients ≥ 65 years of age compared with non-elderly patients < 65 years of age has been suggested. However, as the number of elderly patients ≥ 65 years of age studied was limited and the safety of peramivir has not adequately been evaluated, it is necessary to collect post-marketing safety information regarding the use of peramivir in elderly patients ≥ 65 years of age.

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

4.(iii).B.(3) Clinical positioning

4.(iii).B.(3).1) Clinical positioning of peramivir

PMDA asked the applicant to compare the efficacy and safety etc. of peramivir with those of influenza antiviral agents currently available on the market and then explain the clinical positioning of peramivir.

The applicant responded as follows:

A multiregional phase III study confirmed the non-inferiority of both peramivir 300 mg and 600 mg to oseltamivir phosphate for the time to alleviation of symptoms. Regarding safety, the incidence of adverse drug reactions was significantly lower in the peramivir 300 mg group compared with the oseltamivir phosphate group, demonstrating the higher safety of peramivir 300 mg. Therefore, peramivir offers an additional option for otherwise healthy patients with influenza virus infection and can become a first-choice drug for the treatment of influenza virus infection.

On the other hand, a Japanese phase III study demonstrated the efficacy and safety of intravenous peramivir 600 mg in patients at high risk for severe illness. Especially, patients at high risk for serious illness may have difficulty with an oral or inhaled medication. Thus, intravenous peramivir can be administered easily and reliably even to such patients and peramivir can become a first-choice drug also for the treatment of influenza infections in patients at high risk for severe illness.

Taking account of the fact that the disease is treatable with a single intravenous infusion of peramivir and the results of the oseltamivir phosphate-controlled, multiregional phase III study, PMDA concluded on the clinical positioning of peramivir for the treatment of influenza virus infection as follows:

When choosing a drug from among peramivir and currently available influenza antiviral agents for the treatment of influenza infection, a drug will be chosen according to the patient's condition and drug resistance of circulating influenza viruses, etc. With respect to the clinical positioning of peramivir, since peramivir is characterized by its intravenous route of administration, when compared with currently available influenza antiviral agents, such as oseltamivir phosphate and zanamivir hydrate, as explained by the applicant, peramivir is useful and considered as a first-choice drug for high-risk patients who have difficulty with an oral or inhaled medication. On the other hand, because peramivir is delivered by intravenous infusion, unlike oral and inhaled medications, it will be administered in a medical institution. In the case where peramivir is administered in an outpatient setting, as the disease is treatable with a single

dose of peramivir, peramivir is advantageous in terms of reliable administration without medication compliance problems which are potentially associated with currently available oral and inhaled antiviral medications. However, since patients have to stay in a medical institution for a certain period of time required to receive intravenous peramivir and it is also necessary to be aware of each outpatient clinic's capacity and the risk of nosocomial infection, peramivir is unlikely to be used with the same clinical positioning as oral and inhaled medications. Therefore, if peramivir is considered as an outpatient treatment option, in view of several factors, such as patient medication compliance, tolerability of or adverse reactions to other antiviral agents against influenza, and drug resistance of circulating influenza viruses, an appropriate antiviral agent against influenza should be carefully selected from among oral, inhaled, and intravenously infused medications.

Based on the above, the following caution statement needs to be included in the Precautions for Indications section of the package insert: "The need to administer peramivir should be determined carefully, taking into account that peramivir is delivered by intravenous infusion and considering the use of other oral or inhaled antiviral agents against influenza."

In order to promote the proper use of peramivir, it is recommended that information be made available to medical practices through the development of a guideline for proper use etc., in collaboration with relevant academic societies etc.

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

4.(iii).B.(3).2) Use of peramivir for novel influenza and highly pathogenic avian influenza virus infection

PMDA asked for the applicant's view on the clinical efficacy of peramivir against novel influenza A (H1N1) and highly pathogenic avian influenza A (H5N1) virus infection.

The applicant responded as follows:

Peramivir has never been used for the treatment of novel influenza A (H1N1) or highly pathogenic avian influenza A (H5N1) virus infection in clinical studies and the clinical efficacy of peramivir is unknown.

The US CDC investigated the NA inhibitory activities of currently available influenza antiviral agents and influenza antiviral agents under development for the clinical isolates of novel influenza A (H1N1) virus and reported that (a) peramivir inhibited the NA activity of novel

influenza A (H1N1) virus with an IC_{50} ranging from 0.06 to 0.26 nmol/L, which was similar to its NA IC_{50} (0.16 nmol/L) for seasonal influenza virus and (b) the NA IC_{50} values of oseltamivir carboxylate and zanamivir for novel influenza A (H1N1) virus were 0.28 to 1.41 and 0.30 to 1.34 nmol/L, respectively, which were similar to their NA IC_{50} values for seasonal influenza virus (0.61 and 0.56 nmol/L, respectively) (*MMWR.* 2009 May 1; 58(16): 433-435). The above findings indicate that peramivir exerts anti-viral replication activity *in vivo* based on its *in vitro* NA inhibitory activity also for novel influenza A (H1N1) virus infection. Thus, peramivir is expected to be effective also against novel influenza A (H1N1) virus infection.

The avian influenza virus is an influenza type A virus and HA subtypes 1-16 and NA subtypes 1-9 have been reported to date. The inhibitory activity of peramivir against all NA subtypes N1-N9 was investigated. As a result, peramivir exhibited IC_{50} values of 0.24 to 1.18 nmol/L against all NA subtypes, which were almost comparable to the NA inhibitory activity for ordinary seasonal influenza viruses [see 3.(i).A.(1).2).(j) Activity against highly pathogenic avian influenza viruses]. Therefore, peramivir has been shown to exhibit inhibitory activity independent of antigenicity change among different subtypes. The efficacy of peramivir against highly pathogenic avian influenza A (H5N1) virus was evaluated based on inhibition of NA activity, inhibition of viral shedding, and treatment effectiveness in a lethal murine model of infection with A/Hong Kong/483/97 strain. As a result, the efficacy of peramivir was demonstrated [see 3.(i).A.(1).2).(j) Activity against highly pathogenic avian influenza viruses]. The above results indicate that the clinical efficacy of peramivir against highly pathogenic avian influenza A (H5N1) virus infection is expected.

PMDA considers as follows:
The applicant concluded from the discussion based on non-clinical data that peramivir is expected to be effective against both virus infections, which is understandable. However, because peramivir has never been used for novel influenza A (H1N1) or highly pathogenic avian influenza A (H5N1) virus infection in clinical studies, the clinical efficacy and clinical positioning of peramivir are unknown. Therefore, it is necessary to collect post-marketing information on the clinical efficacy of peramivir against these infections and appropriately provide information to the clinical practice when new evidence becomes available.

4.(iii).B.(4) Dosage and administration

4.(iii).B.(4).1) Dosage and administration of peramivir

The proposed dosage and administration statement is as follows:
“Usually, for adults, 300 mg of peramivir should be administered as a single intravenous

infusion over at least 15 minutes. For patients at high risk for severe illness, 600 mg of peramivir may be administered once daily for up to 5 days. The dosage should be reduced, as appropriate, according to the patient's age and symptoms."

PMDA's view on the dosage and administration of peramivir is as follows:
In Japanese phase II and multiregional phase III studies, peramivir was administered as single doses of 300 mg and 600 mg and there were no differences in the efficacy results between 300 mg and 600 mg of peramivir in either study. Thus, a single 300 mg dose of peramivir can be recommended for patients with influenza virus infection. However, there were no particular differences in safety between single 300 mg and 600 mg doses of peramivir and either dose of peramivir is considered tolerable. Also, an anti-infective agent at a higher dose is preferable unless there is a tolerability problem. Therefore, a 600 mg dose of peramivir may also be chosen for otherwise healthy patients.[45]

On the other hand, since a Japanese phase III study in high-risk patients showed a trend towards a shorter time to alleviation of symptoms in the peramivir 600 mg group compared with the peramivir 300 mg group, peramivir 600 mg is expected to have superior efficacy and there is no problem with recommending a 600 mg dose for high-risk patients. However, as the definition of "patients at high risk for severe illness" as mentioned in the proposed dosage and administration statement is unclear, PMDA asked the applicant to explain the anticipated patient population specifically.

The applicant responded as follows:
According to "Use of influenza A (H1N1) 2009 monovalent vaccine - recommendations of the US Advisory Committee on Immunization Practices (ACIP)" (*MMWR Recomm Rep.* 2009;58:1-8), WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses,[46] and "Guidance on priority groups of patients with medical conditions to receive vaccine for novel influenza,"[47] high-risk groups are defined as (a) people who have underlining medical conditions,[48] (b) pregnant women, (c) children at 1 to 9 years of age, and (d) adults ≥ 65 years of age. Therefore, since the target population for the claimed indication is an adult population, patients with influenza virus infection in high risk

[45] Patients with seasonal influenza viral infections other than those in high risk groups
[46] http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/
[47] http://www.mhlw.go.jp/kinkyu/kenkou/influenza/dl/infu091002-16.pdf
[48] According to MHLW "Guidance on priority groups of patients with underlining medical conditions to receive vaccine for novel influenza," underlining medical conditions include chronic respiratory disease, chronic heart disease, chronic renal disease, chronic hepatic disease, neurologic disease/neuromuscular disease, blood disorders, diabetes, immunocompromised conditions due to disease or medication, and chronic disease in the pediatric field.

groups of (a), (b), and (d) should be classified as “patients at high risk for severe illness.”

Moreover, it is known that both high-risk and otherwise healthy patients can develop severe illness from novel influenza A (H1N1) infection (Japanese Association for Infectious Diseases “Clinical Practice Guideline for Novel Influenza”). Even if patients are not in high risk groups, those who present with symptoms/physical findings that are considered signs of severe illness should be classified as “patients at high risk for severe illness.” Patients infected with high-virulent influenza virus with a high mortality rate, e.g. highly pathogenic avian influenza H5N1 virus, should also be classified as “patients at high risk for severe illness.”

PMDA considers as follows:
Concerning the definition of “patients at high risk for severe illness,” the applicant’s explanation about high risk groups is largely acceptable and there is no particular problem with recommending “600 mg once daily for patients at high risk for severe illness” in the package insert. However, it is necessary to continue to collect post-marketing information on the efficacy of peramivir 600 mg QD in high-risk patients other than those eligible for inclusion in the Japanese phase III study (patients with poorly controlled diabetes, patients with chronic respiratory disease requiring pharmacotherapy, patients currently on immunosuppressant medication). On the other hand, although non-clinical studies indicate that the efficacy of peramivir is expected in patients with novel influenza A (H1N1) or highly pathogenic avian influenza virus infection who were classified by the applicant as “patients at high risk for severe illness” [see 4.(iii).B.(3).2) Use of peramivir for novel and highly pathogenic avian influenza virus infections], as there is no clinical experience with peramivir, it is necessary to appropriately provide information to medical practices.

It is anticipated that peramivir 600 mg may be administered to patients who have already developed severe influenza virus infection. However, no clinical study in patients with severe influenza illness has been conducted and no peramivir efficacy data are available. Meanwhile, according to the information obtained from the applicant, foreign phase III studies to evaluate the efficacy of peramivir 600 mg administered QD for 5 days in patients who are hospitalized due to influenza viral infections (Studies BCX1812-301 and BCX1812-303) are under planning and the results from these foreign clinical studies will serve as reference data on the efficacy of peramivir 600 mg in patients with severe influenza virus infection. Therefore, when the results of these foreign phase III studies under planning (Studies BCX1812-301 and BCX1812-303) become available, it is necessary to provide the obtained information to medical practices.

As to the number of doses received, based on the discussion in "4.(iii).B.(1).4) Efficacy in high-risk patients," the time to alleviation of symptoms is expected to be shorter in multiple-dosed patients, compared with single-dosed patients. In the Japanese phase III study, although peramivir was allowed to be administered for up to 5 days,actually, of 37 subjects, 10 subjects received a single dose, 23 subjects were treated for 2 days, 2 subjects were treated for 3 days, 1 subject was treated for 4 days, and 1 subject was treated for 5 days. Thus, the need to administer peramivir for ≥ 3 days is unclear. However, when peramivir is made available to the medical practice, peramivir is expected to be used in a broader range of high-risk patients compared to the study population and it can not be excluded that there will be patients who need to receive peramivir for up to 5 days. Therefore, it is necessary to collect information on patients treated with peramivir for ≥ 3 days as to patient demographics and the efficacy and safety of peramivir via post-marketing surveillance etc. and continue to evaluate the significance of multiple dose administration for ≥ 3 days. Multiple dose administration is not required for all patients and multiple doses of peramivir should not be unnecessarily continued without careful consideration. As with the criteria for continuing treatment from Day 2 onward as specified in the clinical study, it should be stated in the precautions of dosage and administration section of the package insert that "treatment with peramivir should be continued only if body temperature is ≥ 37.5°C, or if treatment continuation is judged necessary based on clinical symptoms even in the case where body temperature is < 37.5°C." Treatment continuation should be decided according to the symptoms so that treatment with peramivir will not be continued without careful consideration.

Based on the above, as a 600 mg dose may also be chosen for otherwise healty patients, the appropriateness of dosage and administration will be discussed at the Expert Discussion.

4.(iii).B.(4).2) Dosage and administration for patients with renal impairment

The applicant explained that peramivir may be administered to patients with mild renal impairment (CLcr 50-80 mL/min) at the same dosage regimen as for patients with normal renal function (CLcr ≥ 80 mL/min) and no dose adjustment is required.

Since peramivir plasma concentrations tended to increase in subjects with mild renal impairment and body weight affects peramivir plasma concentrations and plasma concentrations tend to increase in low-body-weight patients [see 4.(ii) Summary of clinical pharmacology studies], PMDA asked the applicant to explain whether dose adjustment is required for low-body-weight patients with mild renal impairment.

The applicant responded as follows:
The simulated C_{max} following an intravenous infusion of peramivir 600 mg over 15 minutes in low-body-weight (30-50 kg) patients with mild renal impairment is considered to be within the C_{max} range following a single dose of peramivir 800 mg that has been demonstrated to be tolerable and safe in a Japanese phase I study (Study [redacted]14T0612) [see 4.(ii) Summary of clinical pharmacology studies]. Thus, no dose adjustment is required for low-body-weight patients with mild renal impairment.

PMDA considers as follows:
Based on the simulation results, the (predicted) C_{max} following a single intravenous dose of peramivir 600 mg is unlikely to deviate from the C_{max} range following a single 800 mg dose (15-minute infusion) that has been demonstrated to be safe in healthy adults and the applicant's response that no dose adjustment is required for these patients is acceptable. However, considering inter-individual variability in pharmacokinetics, caution is needed for possible safety risks associated with increased exposure (C_{max}) when administering peramivir to low-body-weight patients with mild renal impairment.

4.(iii).B.(5) Indication
Based on the above discussions in "4.(iii).B.(1) Efficacy and 4.(iii).B.(2) Safety," PMDA concluded that there is no problem with the proposed indication of "influenza A or B virus infection."

However, as the efficacy of peramivir against the H275Y mutant virus is undefined, it is necessary to actively collect post-marketing information on the clinical efficacy of peramivir against infections with influenza viruses containing drug resistance mutations, e.g., H275Y mutant virus and provide information to medical practices when new evidence becomes available. Since the use of an influenza antiviral agent should be determined according to the information on drug resistance of circulating influenza viruses, it should be stated in the Precautions for indications section of the package insert that "the appropriateness of the use of peramivir should be determined, taking account of the information on drug resistance of circulating viruses in each season" etc.

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

4.(iii).B.(6) Pediatric indication
Concerning the status of development of peramivir for pediatric influenza viral infections,

PMDA confirmed that a Japanese phase III study in pediatric patients is currently ongoing.

Synopsis of Japanese phase III study in pediatric patients

Study population	Pediatric patients with influenza A or B virus infections aged 28 days to less than 16 years
Study design	A multicenter, uncontrolled, open-label study to evaluate the efficacy, safety, and pharmacokinetics of peramivir 10 mg/kg administered as an intravenous infusion QD for 1-5 days
Target sample size	100 subjects

4.(iii).B.(7) Post-marketing surveillance etc.

The applicant stated that as post-marketing investigations, no drug use-results survey is planned and special drug use-results surveys of pregnant women/nursing mothers and of patients with decreased physical function (300 subjects, central registration system, 2 years duration) are being planned.

PMDA asked for the applicant's view on the important identified risks of peramivir, important potential risks, and important missing information.

The applicant responded as follows:

As the important identified risks of peramivir, white blood cell count decreased and neutrophil count decreased reported as adverse drug reactions in clinical studies have been identified. The important potential risks of peramivir, though not reported in clinical studies of peramivir, include anaphylactoid reactions listed in the package inserts for other drugs of the same class, i.e., oseltamivir phosphate and zanamivir hydrate, and neuropsychiatric symptoms (consciousness disturbance, abnormal behavior, delirium, hallucination, delusion, convulsion, etc.) listed in the package insert for oseltamivir phosphate, and caution is needed with peramivir as well. The important missing information include the safety of peramivir in the elderly, patients with renal impairment, patients with hepatic impairment, patients with decreased physical function, children, and pregnant women/nursing mothers.

PMDA considers as follows:

It is necessary to collect the following information via post-marketing surveillance etc., apart from the above safety issues listed by the applicant.

- Differences in safety profile between single-dosed and multiple-dosed patients
- Diarrhoea, nausea, AST increased, ALT increased, and white blood cell count decreased that occurred more frequently in the peramivir 600 mg group than in the peramivir 300 mg group

Furthermore, based on the discussions in "4.(iii).B.(1) Efficacy, 4.(iii).B.(3) Clinical positioning, 4.(iii).B.(4) Dosage and administration, and 4.(iii).B.(5) Indication," it is necessary to collect information on the efficacy of and resistance to peramivir via post-marketing surveillance, such as:

- The efficacy of peramivir against influenza B virus infection, which was evaluated in a limited number of patients in clinical studies
- The efficacy of peramivir in patients infected with influenza viruses with an amino acid substitution, e.g., H275Y mutation
- The safety and efficacy of peramivir 600 mg in high-risk patients (including high-risk patients other than those eligible for inclusion in a Japanese phase III study)
- The safety and efficacy of peramivir 600 mg QD in patients with severe influenza virus infection
- Patient demographics and the safety and efficacy of peramivir in patients treated with peramivir for ≥ 3 days
- The efficacy of peramivir in patients with novel influenza A (H1N1) or highly pathogenic avian influenza virus infection
- Information on influenza virus resistance to peramivir

In view of the above points, the post-marketing plan needs to be reviewed.

The above conclusion of PMDA and other issues for consideration will be discussed at the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspection and data integrity assessment

To be reported later.

2. PMDA's conclusion on the results of GCP on-site inspection

To be reported later.

IV. Overall Evaluation

As a result of its review based on the submitted data, PMDA concluded on the efficacy and safety of peramivir as follows:

Since a Japanese phase II study confirmed the superiority of peramivir over placebo and a multiregional phase III study confirmed the non-inferiority of peramivir to oseltamivir phosphate, although the efficacy of peramivir against the H275Y mutant virus is undefined, the efficacy of peramivir against influenza viral infections has been confirmed. The safety of peramivir is acceptable in view of its observed benefits.

Furthermore, peramivir has clinical significance because it is delivered by intravenous infusion and can be used in patients who have difficulty with an oral or inhaled medication. Because peramivir is a drug with a new active ingredient, it is necessary to continue to collect post-marketing information on the safety and efficacy of peramivir.

Taking account of the current pandemic of novel influenza A (H1N1) in Japan and overseas as of November 2009 and the above-mentioned clinical significance of peramivir, a survey over a certain period of time, covering all patients treated with peramivir, should be conducted to identify treated patients and actual use when peramivir has been made available to clinical practice and collect safety information. Such a suvey needs to be imposed as a condition for approval.

The following points should be further discussed at the Expert Discussion. Then, if it can be concluded that there are no particular problems, peramivir may be approved.

[Issues to be discussed at the Expert Discussion]

- Efficacy
- Safety
- Clinical positioning
- Dosage and administration
- Indication
- Post-marketing investigations

Review Report (2)

December 16, 2009

1. Product Submitted for Registration

[Brand name]	(a) Rapiacta 300 mg bag for intravenous drip infusion
	(b) Rapiacta 150 mg vial for intravenous drip infusion
[Non-proprietary name]	Peramivir Hydrate
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	October 30, 2009

2. Content of the Review

The Pharmaceuticals and Medical Devices Agency (PMDA) sought the expert advisors' comments based on the Review Report (1).[49] Discussions with the expert advisors are summarized below.

The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

1) Efficacy

Based on the submitted clinical study data, PMDA concluded on the efficacy of peramivir against influenza viral infections as follows:

Since (a) a Japanese phase II study in patients with seasonal influenza infections confirmed the superiority of peramivir over placebo and (b) a multiregional phase III study confirmed the non-inferiority of peramivir to oseltamivir phosphate, although the efficacy of peramivir against some strains of viruses with an amino acid substitution in NA, e.g., the H275Y mutant virus, is undefined, the efficacy of peramivir against influenza viral infections has been confirmed. As to the efficacy of peramivir by influenza viral type, since (a) the efficacy of peramivir against influenza A (H1N1) virus harbouring the H275Y mutation is undefined and (b) the number of patients with influenza B virus infection studied is limited and rigorous evaluation is difficult, it

[49] The Expert Discussion on the product took place to discuss with the expert advisors based on the Review Report 1. In addition, the information on a pediatric clinical study as of [redacted] was also discussed with the expert advisors on another occasion.

is necessary to continue to collect post-marketing information on the efficacy of peramivir against the H275Y mutant and influenza B virus infection.

The above conclusion of PMDA was largely supported by the expert advisors. Moreover, the following comments were raised from the expert advisors: although the results of the multiregional phase III study confirmed that the efficacy of peramivir is not inferior to that of oseltamivir phosphate, the efficacy of peramivir against strains of influenza A (H1N1) virus, most of which contained the H275Y mutation, is inconclusive; and information should be provided with caution so as to avoid excessive expectations for the efficacy of peramivir, e.g. it has superior efficacy over currently available influenza antiviral agents.

PMDA considers as follows:
As the multiregional phase III study included no placebo group, it is difficult to rigorously evaluate the efficacy of peramivir against the H275Y mutant virus. Given the above comments from the expert advisors, the results of clinical studies of peramivir should be interpreted carefully and the information on the efficacy data of peramivir (e.g., the efficacy of peramivir against the H275Y mutant virus is undefined) should be appropriately provided to medical practices. At the same time, it should be advised to determine the appropriateness of the use of peramivir carefully prior to its use, taking account of the information on drug resistance of circulating viruses.

2) Efficacy in high-risk patients

PMDA concluded on the results from a Japanese phase III study in high-risk patients as follows: Since (a) the median time to alleviation of symptoms (90% CI) in the peramivir groups combined was 92.0 hours (14.6, 235.3) in single-dosed subjects and 64.1 hours (41.5, 111.2) in subjects treated for ≥ 2 days and (b) the median time to alleviation of symptoms (90% CI) in multiple-dosed subjects was 111.2 hours (40.2, 123.1) in the peramivir 300 mg group and 42.7 hours (30.3, 103.3) in the peramivir 600 mg group, although rigorous comparison is difficult, a trend towards a shorter time to alleviation of symptoms following multiple dose administration of peramivir 600 mg compared with 300 mg has been suggested.

The above conclusion of PMDA was largely supported by the expert advisors. Meanwhile, the following comments were raised from the expert advisors: it is difficult to conclude based only on the Japanese phase III study in high-risk patients that peramivir 600 mg is expected to be more effective than 300 mg; and in order to recommend peramivir 600 mg for high-risk patients, the conduct of a clinical study to confirm the efficacy of peramivir 600 mg in these patients may

be needed.

Taking account of the above comments from the expert advisors, PMDA considers as follows: Given that there are patients who need an influenza antiviral agent for intravenous infusion in clinical practice and its rapid development is desired, although the currently available information is limited, it is of great significance to make peramivir available to clinical practice faster rather than spend further time in development by conducting an additional clinical study to confirm the efficacy of peramivir 600 mg in high-risk patients. Therefore, since the results of the Japanese phase III study suggested a trend towards a shorter time to alleviation of symptoms with peramivir 600 mg compared with 300 mg in high-risk patients, it may be concluded that peramivir 600 mg has been demonstrated to be more effective than peramivir 300 mg in high-risk patients. However, it is necessary to continue to collect post-marketing information on the efficacy and safety of peramivir 600 mg in high-risk patients.

The above conclusion of PMDA was supported by the expert advisors.

(2) Safety

1) Overall safety

PMDA concluded on the safety of peramivir as follows:

Since (a) there were no clinically meaningful differences in the incidence of adverse events or adverse drug reactions between peramivir 300 mg or 600 mg and placebo in a Japanese phase II study and (b) there was no major problem with the tolerability of peramivir 300 mg or 600 mg and the incidence of adverse events or adverse drug reactions was not higher in the peramivir group compared with the oseltamivir phosphate group in a multiregional phase III study, there are no particular problems with increasing dose. Because the incidences of diarrhoea, nausea, ALT increased, white blood cell count decreased, and AST increased, both as adverse events and as adverse drug reactions, tended to be higher in the peramivir 600 mg group than in the peramivir 300 mg group, the possible occurrence of these events should be kept in mind.

The above conclusion of PMDA was supported by the expert advisors.

2) Safety of multiple-dose peramivir in high-risk patients

PMDA considers that the results of a Japanese phase III study in high-risk patients showed no trend towards an increase in the risk of clinically relevant adverse events with multiple-dose peramivir. However, as the safety information on multiple-dose peramivir is limited [especially, the number of subjects who received at least 3 doses was 5 (300 mg, 3 subjects; 600 mg, 2

subjects)], PMDA concluded that the need for multiple dose administration should be carefully determined based on the patient's symptoms etc. and it is necessary to collect post-marketing information on safety in patients who received at least 3 doses of peramivir and on differences in safety profile between single-dosed and multiple-dosed patients.

There was a comment from the expert advisors that since the information on safety in patients who received at least 3 doses of peramivir included in the submitted data is insufficient and whether the risk of adverse events is increased is unknown, it is necessary to collect further information after the market launch. The above conclusion of PMDA was supported by the expert advisors.

(3) Clinical positioning

PMDA considers that peramivir, which is delivered by intravenous infusion, is useful for patients who have difficulty with an oral or inhaled medication and is advantageous in terms of more reliable administration in patients with potential poor compliance, as the disease is treatable with a single dose of peramivir. However, when peramivir is considered as an outpatient treatment option, it is necessary to be aware of each outpatient clinic's capacity and possible nosocomial infection, as patients have to stay in a medical institution for a certain period of time required to receive intravenous peramivir. Therefore, PMDA concluded that when the use of peramivir in an outpatient setting is considered, in view of patient medication compliance, tolerability of or previous adverse reactions to other antiviral agents against influenza, drug resistance of circulating influenza viruses, etc., an appropriate antiviral agent against influneza should be carefully selected from among oral and inhaled medications and peramivir for intravenous infusion.

In order to promote the proper use of peramivir, PMDA recommends that the applicant should cooperate and collaborate with relevant academic societies etc., promptly develop a guideline for proper use etc., and provide information to the medical practice.

The above conclusion of PMDA was supported by the expert advisors.

(4) Dosage and administration

The proposed dosage and administration statement is as shown below. Since patients in high-risk groups are at high risk for severe illness, e.g., exacerbation/relapse of their underlining medical conditions and occurrence of complications, the applicant conducted a Japanese phase III study in high-risk patients in which peramivir was allowed to be administered as a single or

multiple doses and proposed a dosage regimen for patients at high risk for severe illness separately from that for otherwise healthy patients with influenza virus infection.

Usually, for adults, 300 mg of peramivir should be administered as a single intravenous infusion over at least 15 minutes.
For patients at high risk for severe illness, 600 mg of peramivir may be administered once daily for up to 5 days.
The dosage should be reduced, as appropriate, according to the patient's age and symptoms.

1) Dosage and administration for otherwise healthy patients with influenza virus infection
As there were no differences in efficacy between single doses of 300 mg and 600 mg of peramivir in Japanese phase II and multiregional phase III studies, PMDA considers that a single dose of 300 mg may be recommended for otherwise healthy patients with influenza virus infection. On the other hand, there were no particular differences in safety between peramivir 300 mg and 600 mg and either dose of peramivir is considered tolerable. Also, an anti-infective agent at a higher dose is preferable unless there is a tolerability problem. Thus, PMDA considers that a single dose of 600 mg may also be chosen for otherwise healthy patients with influenza virus infection.

There was a comment from the expert advisors that since the currently available information shows little evidence suggesting that a single dose of 600 mg is more useful, the appropriate dosage regimen for otherwise healthy patients with influenza virus infection should be a single dose of 300 mg. On the other hand, it was also commented that a single dose of 600 mg should be recommended in view of the possibility that non-high-risk patients may also develop severe illness from influenza.

PMDA concluded as follows:
Based on the submitted clinical study data, the following findings were noted: (a) there were no apparent differences in efficacy between 300 mg and 600 mg of peramivir in otherwise healthy patients with influenza virus infection and (b) no pharmacokinetic parameters etc. that correlates with the therapeutic efficacy of an influenza antiviral agent have been identified, which means that at present, there is no adequate evidence for recommending a single dose of 600 mg. Therefore, the appropriate dosage regimen for otherwise healthy patients with influenza virus infection is a single dose of 300 mg.

2) Dosage and administration for high-risk patients

Taking also account of the expert advisors' comment on the need to confirm the efficacy of peramivir 600 mg [see "(1) Efficacy"], PMDA concluded as follows:

Since (a) a trend towards a shorter time to alleviation of symptoms with multiple doses of 600 mg of peramivir compared with a single dose of 300 mg in high-risk patients has been suggested and (b) an increase in clinically relevant safety risk with peramivir 600 mg compared with 300 mg has not been suggested, in view of the balance between the risks and benefits, 600 mg may be chosen as the dose of peramivir for high-risk patients. However, although peramivir was allowed to be administered for up to 5 days in a Japanese phase III study, most patients actually received a single dose or were treated for 2 days (of 37 subjects, 10 subjects received a single dose, 23 subjects were treated for 2 days, 2 subjects were treated for 3 days, 1 subject was treated for 4 days, 1 subject was treated for 5 days). Thus, the need for multiple dose administration for ≥ 3 days has not adequately been defined by the submitted study data.

The following comments were raised from the expert advisors: (a) the definition of "patients at high risk for severe illness" is unclear and it may be difficult to select appropriate patients; (b) as the number of patients treated for ≥ 3 days was limited in the Japanese phase III study, there is little evidence for recommending administration for up to 5 days; and (c) body temperature ≥ 37.5°C as the criterion for multiple dose administration is not sufficiently justified.

Taking account of the above comments from the expert advisors, PMDA concluded as follows:

Since a 600 mg dose of peramivir for "patients at high risk for severe illness" is based on the results of the Japanese phase III study, the appropriate wording should be "patients at high risk for severe influenza complications etc." to define the intended population more specifically. As there is limited experience with multiple dose administration for ≥ 3 days, the maximum recommended duration of treatment should not be specified in the Dosage and Administration section of the package insert and it should be stated in the Precautions for dosage and administration section of the package insert that the need for multiple dose administration should be carefully determined according to the patient's symptoms. Moreover, "body temperature ≥ 37.5°C" as the criterion for multiple dose administration is set out in accordance with the criteria for continuing treatment in the Japanese phase III study and there is no clear evidence that a threshold of 37.5°C is appropriate. Therefore, it should be stated that "multiple doses should be administered if treatment continuation is judged necessary according to clinical symptoms such as body temperature. Note that there is limited experience with multiple dose administration for ≥ 3 days [see "Clinical Studies"]."

Based on the above review, PMDA concluded that the appropriate dosage and administration statement is as follows.

"Usually, for adults, 300 mg of peramivir should be administered as a single intravenous infusion over at least 15 minutes. For patients at high risk for severe influenza complications etc., 600 mg of peramivir should be administered as an intravenous infusion over at least 15 minutes, but once-daily multiple doses of 600 mg may be administered according to the patient's symptoms. The dosage should be reduced, as appropriate, according to the patient's age and symptoms."

(5) Indication

Based on the submitted study data, PMDA concluded as follows:

The proposed indication of "influenza A or B virus infection" is acceptable. However, since the efficacy of peramivir against the H275Y mutant virus is undefined, it is necessary to actively collect post-marketing information and provide the information appropriately to the medical practice when evidence becomes available. As to the information on drug resistance of influenza viruses, it should be stated in the Precautions for indications section of the package insert that "the appropriateness of the use of peramivir should be determined, taking account of the information on drug resistance of circulating viruses."

The above conclusion of PMDA was supported by the expert advisors.

(6) Post-marketing investigations

The applicant explained the important identified risks of peramivir, important potential risks, and important missing information as follows:

- Important identified risks of peramivir: white blood cell count decreased and neutrophil count decreased reported as adverse drug reactions in clinical studies
- Important potential risks of peramivir: anaphylactoid reactions listed in the package inserts for other drugs of the same class, i.e., oseltamivir phosphate and zanamivir hydrate, though not reported in clinical studies of peramivir; and neuropsychiatric symptoms listed in the package insert for oseltamivir phosphate (consciousness disturbance, abnormal behavior, delirium, hallucination, delusion, convulsion, etc.)
- Important missing information: the safety of peramivir in the elderly, patients with renal impairment, patients with hepatic impairment, patients with decreased physical function,

children, and pregnant women/nursing mothers

PMDA considers that it is necessary to collect the following information via post-marketing surveillance etc., in addition to the above points. Taking account of the Japanese and overseas situations surrounding influenza infections, e.g., the ongoing pandemic of novel influenza A (H1N1), and the clinical significance of the route of administration (i.e., intravenous infusion) of peramivir, it is necessary to identify usage conditions and collect safety information over a certain period of time, covering all patients treated with peramivir, in order to identify treated patients and usage conditions and take necessary action for the proper use of peramivir.

- Differences in safety profile between single-dosed and multiple-dosed patients
- Diarrhoea, nausea, AST increased, ALT increased, and white blood cell count decreased that occurred more frequently in the peramivir 600 mg group than in the peramivir 300 mg group
- The efficacy of peramivir against influenza B virus infection, which was evaluated in a limited number of patients in clinical studies
- The efficacy of peramivir against influenza viruses with an amino acid substitution, e.g., H275Y mutation
- The safety and efficacy of peramivir 600 mg in high-risk patients (including high-risk patients other than those eligible for inclusion in a Japanese phase III study)
- The safety and efficacy of peramivir in patients with severe influenza virus infection
- Patient demographics and the safety and efficacy of peramivir in patients treated for ≥ 3 days
- The efficacy of peramivir in patients with novel influenza A (H1N1) or highly pathogenic avian influenza virus infection
- Information on influenza virus resistance to peramivir

The above conclusion of PMDA was supported by the expert advisors.

PMDA instructed the applicant to collect post-marketing information, taking account of the above points and identify usage conditions and collect safety information over a certain period of time, covering all patients treated with peramivir, when peramivir has been made available to clinical practice.

The applicant responded that they will identify usage conditions and collect safety information, covering all patients treated with peramivir, for 6 months after the market launch and conduct a

specified drug use-results survey of high-risk patients (people with underlining medical conditions,[50] pregnant women, adults ≥ 65 years of age) (Target sample size of 600), a survey of pregnant women/nursing mothers, a survey on novel influenza virus infection, and a survey for collecting the information on influenza virus resistance to peramivir.

In addition to the applicant's proposals, PMDA instructed the applicant to actively collect information on the efficacy of peramivir against influenza B and the H275Y mutant influenza virus infections, which was not adequately evaluated in the clinical studies submitted, such as by investigating the nonclinical anti-viral activity of peramivir, collecting information on the clinical efficacy of peramivir from the published literature etc., and considering the conduct of a separate survey etc. according to the epidemic status of influenza virus.

The applicant responded as follows:
In order to evaluate the efficacy of peramivir against influenza B and the H275Y mutant influenza virus infections, (a) an investigation will be conducted until sufficient data on the *in vitro* anti-viral activity of peramivir are collected and (b) relevant cases will be identified from post-marketing surveys etc. under planning to evaluate the clinical efficacy of peramivir and the epidemic status of influenza virus, while cases reported in the literature etc. will be carefully watched and the conduct of a separate post-marketing survey etc. will be considered as appropriate.

PMDA accepted the applicant's response.

(7) Children

As of [redacted], a Japanese phase III study in pediatric patients with influenza virus infection (pediatric phase III study) is ongoing (see the table below).

Synopsis of pediatric phase III study

Study population	Pediatric patients with influenza A or B virus infection aged 28 days to less than 16 years
Study design	A multicenter, uncontrolled, open-label study to evaluate the efficacy, safety, and pharmacokinetics of peramivir 10 mg/kg administered as an intravenous infusion QD for 1-5 days
Dosage regimen	10 mg/kg (600 mg for patients weighing ≥ 60 kg) once daily for 1-5 days
Study period	Ongoing (as of [redacted]) - started in [redacted]
Target sample size	100 subjects

[50] Underlining medical conditions include chronic respiratory disease, chronic heart disease, chronic renal disease, chronic hepatic disease, neurologic disease/neuromuscular disease, blood disorders, diabetes, immunocompromised conditions due to disease or medication, and chronic disease in the pediatric field.

As an interim report on the pediatric phase III study, the information from 105 subjects enrolled during the first 2 months of the study was submitted by the applicant. The interim report on this study has not been subject to GCP inspection.[51]

The applicant explained the efficacy and safety information from 105 subjects as follows:
The mean age of subjects was 9.8 years (range, 2-15 years) and all of the 105 subjects were diagnosed with influenza A by rapid influenza diagnostic test and 97 of the 105 subjects were outpatients. As to the number of doses received, 97 subjects received a single dose and 8 subjects received 2 doses.

The observed plasma drug concentrations in pediatric patients with influenza virus infection[52] were within the plasma drug concentration range following the administration of peramivir 300 or 600 mg to adult influenza patients and did not exceed the mean plasma drug concentration following the administration of peramivir 800 mg to healthy adult subjects.

The primary efficacy endpoint of the median time to alleviation of symptoms[53] (95% CI) was 27.7 hours (21.7, 31.7) in the overall population, 26.4 hours (17.8, 68.9) in subjects aged 2 to 5 years, 25.6 hours (20.8, 31.7) in subjects aged 6 to 11 years, and 29.1 hours (20.9, 36.3) in subjects aged 12 to 15 years.

Regarding safety, the incidence of adverse events was 59.0% (62 of 105 subjects) and the incidence of adverse drug reactions was 27.6% (29 of 105 subjects). Adverse events reported by at least 2 subjects were neutrophil count decreased (16.2% [17 of 105 subjects]), diarrhoea (15.2% [16 of 105 subjects]), vomiting (10.5% [11 of 105 subjects]), eosinophil count increased (8.6% [9 of 105 subjects]), urine ketone body present (3.8% [4 of 105 subjects]), abnormal behavior (2.9% [3 of 105 subjects]), abdominal pain (1.9% [2 of 105 subjects]), nausea (1.9% [2 of 105 subjects]), and white blood cell count decreased (1.9% [2 of 105 subjects]). Adverse drug reactions reported by at least 2 subjects were diarrhoea (9.5% [10 of 105 subjects]), neutrophil count decreased (6.7% [7 of 105 subjects]), vomiting (5.7% [6 of 105 subjects]), eosinophil count increased (3.8% [4 of 105 subjects]), nausea (1.9% [2 of 105 subjects]), and white blood cell count decreased (1.9% [2 of 105 subjects]). Three serious adverse events

[51] PMDA has not assessed the integrity of the submitted data.
[52] Data from 110 subjects whose plasma drug concentrations were obtained within the first 2.5 months of the study (0 to < 2 years of age, 6 subjects; 2 to < 6 years of age, 21 subjects; 6 to < 16 years of age, 83 subjects) were used.
[53] Time to alleviation of symptoms defined as time to resolution of influenza symptoms. The following (a) and (b) had to be met and continue for at least 21.5 hours.
(a) "Cough" and "runny nose/nasal congestion" were both "0: absent" or "1: mild" based on patient diary entries.
(b) Body temperature (axillary temperature) was < 37.5°C.

occurred in 2 subjects (a 6-year-old child and a 5-year-old child[54]) (influenza with pneumonia; pneumonia and influenza encephalopathy), but a causal relationship to peramivir was denied and the outcome was reported as “recovered” for all events. No deaths were reported.

Adverse events not reported by adults were abnormal behavior (3 subjects, 3 events), pyrexia (1 subject, 1 event), joint sprain (1 subject, 1 event), and encephalopathy (1 subject, 1 event). Abnormal behavior occurred in 3-, 11-, and 12-year-old children on the day of study drug administration or on the day following study drug administration and all of these subjects had a fever in the 39 to < 40°C range. Abnormal behavior was mild in severity with an outcome of “recovered” for all 3 cases and its causal relationship to study drug was denied except for the event in the 3-year-old child.

Based on the above, there has so far been no particular problem with the safety of peramivir in pediatric patients with influenza virus infection.

PMDA confirmed that the plasma drug concentrations at a dose of 10 mg/kg of peramivir in pediatric patients with influenza virus infection were within the plasma drug concentration range following the administration of peramivir at a dose of 300 or 600 mg to adult patients and did not exceed the mean plasma drug concentration at a dose of 800 mg of peramivir that has been demonstrated to be tolerable in adults in a phase I clinical study.

PMDA asked the applicant to explain differences in the safety of peramivir between children and adults.

The applicant responded as follows:
The incidences of adverse events and adverse drug reactions in the peramivir groups combined in 2 adult-controlled studies (Japanese phase II and multiregional phase III studies) were 56.3% and 24.3%, respectively, which were not particularly different from those in the pediatric phase III study (59.0% and 27.6%, respectively). Adverse events with a higher incidence in children than in adults were neutrophil count decreased (8.4% in adults, 16.2% in children), diarrhoea (9.0% in adults, 15.2% in children), vomiting (1.2% in adults, 10.5% in children), eosinophil count increased (0.2% in adults, 8.6% in children), and urine ketone body present (1.0% in adults, 3.8% in children). Adverse events not reported by adults were abnormal behavior [3], pyrexia [1], joint sprain [1], and encephalopathy [1], most of which have been suggested to be

[54] This subject (pneumonia and influenza encephalopathy) was diagnosed with novel influenza A (H1N1) by PCR assay.

potentially associated with influenza virus infection, but it is necessary to continue to carefully watch for the possible occurrence of these events.

PMDA asked the applicant to explain the risk of psychiatric disorders/neurologic symptoms, e.g., abnormal behavior, following the administration of peramivir to children.

The applicant responded as follows:
Psychiatric disorders and nervous system disorders reported so far in the pediatric phase III study were encephalopathy in 1 subject and abnormal behavior in 3 subjects. Encephalopathy is a rare complication of influenza viral infection in children and is considered to be caused by the overproduction of inflammatory cytokines. However, as peramivir does not have the pharmacological property of producing inflammatory cytokines, peramivir is not associated with the risk of encephalopathy. Abnormal behavior occurred with a high fever in the 39 to < 40°C range in the early phase of influenza viral infection for all of the 3 cases. Abnormal behavior has also been reported by even patients untreated with an influenza antiviral agent who had a high fever. Therefore, abnormal behavior reported in the pediatric phase III study is also likely to be a symptom associated with influenza virus infection. However, though a causal relationship is unknown, abnormal behavior has been reported with other drugs of the same class. At present, there is no accumulated information sufficient to deny the risk of abnormal behavior associated with peramivir. Thus, it is necessary to continue to collect and analyze post-marketing safety information.

PMDA considers as follows:
According to the information from the pediatric phase III study, no major problems with the safety of peramivir in children have been suggested so far, except for abnormal behavior that was not reported by adults occurred and neutrophil count decreased, diarrhoea, vomiting, eosinophil count increased, and urine ketone body present occurred more frequently in children than in adults.

However, with respect to the occurrence of abnormal behavior, although the applicant's conclusion (a causal relationship of abnormal behavior to peramivir was denied for 2 of the 3 cases in the pediatric phase III study and abnormal behavior is likely to be a symptom associated with influenza virus infection) is understandable. However, since (a) the applicant's conclusion is based on the limited information currently available from the pediatric phase III study, (b) a causal relationship of abnormal behavior to a therapeutic drug can not always be determined definitively, and (c) the package inserts for other drugs of the same class caution

about possible abnormal behavior in patients in their teens who are receiving the drug, it is necessary to continue to watch for the possible occurrence of abnormal behavior in children treated with peramivir as well. Meanwhile, although a safety pharmacology study assessing the effects of peramivir on the central nervous system showed increased landing foot splay in rats, the applicant discussed that peramivir is unlikely to affect the central nervous system in clinical use on the basis of the following findings: (1) there were no effects on other general symptoms and behavior; (2) the baseline value of landing foot splay in the 100 mg/kg group was higher than that in the control group, resulting in significant differences; and (3) the event occurred at a plasma concentration approximately 5-fold higher than that following a single intravenous dose of 800 mg of peramivir in Japanese adult male subjects. PMDA considers that the applicant's discussion is understandable [see the Review Report (1), 3.(i).A.(3) Safety pharmacology].

It has been suggested that neutrophil count decreased, diarrhoea, vomiting, eosinophil count increased, and urine ketone body present may occur more frequently in children than in adults, which needs to be kept in mind.

Furthermore, the safety information from 12 subjects (0-year-old children, 4 subjects; 1-year-old children, 8 subjects) enrolled in the pediatric phase III study between 2 months after the start date and the date of last patient enrollment[55] was additionally submitted by the applicant on [redacted]. No serious adverse events were reported among the 12 subjects and adverse events occurred in three 0-year-old children (6 events)[56] (loose stools [2], right occipital swelling [1], abdominal eczema [1], rhinorrhoea [1], rash [1]) and in two 1-year-old children (2 events) (neutrophil count decreased [1], upper respiratory tract inflammation [1]) and a causal relationship to study drug could not be denied for 1 case of loose stools (0-year-old child) and 1 case of neutrophil count decreased (1-year-old child). PMDA confirmed that no particular problems with the safety of peramivir in 0-year-old and 1-year-old children have so far been suggested.

PMDA considers that as peramivir is very likely to be used in children when peramivir has been made available to medical practice, the information on the ongoing pediatric phase III study needs to be provided via the package insert and other material.

The above conclusion of PMDA was supported by the expert advisors.

[55] Extracted data up to 7 days after last patient enrollment. Source data verification has not been performed.
[56] Extracted data up to 10 days after last patient enrollment. Source data verification has not been performed.

PMDA instructed the applicant to provide the information on the pediatric phase III study via the package insert etc. As a result, the information as of November 27, 2009 was included in the clinical studies section of the package insert.

3. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

(1) PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

(2) PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (CTD, 5.3.5.1-01, 5.3.5.2-01, 5.3.5.1-02). As a result, although some medical institutions did not sign a contract with a site management organization (SMO) to transfer part of trial-related duties and protocol deviations (enrollment of subjects who met the exclusion criteria) were found at some trial sites, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

4. Overall Evaluation

Based on the above review, PMDA considers as follows:

Since (a) a Japanese phase II study in patients with seasonal influenza infections has confirmed the superiority of peramivir over placebo and (b) a multiregional phase III study has confirmed the non-inferiority of peramivir to oseltamivir phosphate, although the efficacy of peramivir against some strains of viruses with an amino acid substitution in NA, e.g., H275Y mutant virus, is undefined, the efficacy of peramivir against influenza viral infections has been confirmed. Regarding safety, although peramivir is considered tolerable based on the submitted data, it is necessary to continue to collect post-marketing information, as there is no sufficient information on the safety of multiple-dose peramivir.

Taking account of the Japanese and overseas situations surrounding influenza infections, e.g., the ongoing pandemic of novel influenza A (H1N1), and the clinical significance of the route of

administration (i.e., intravenous infusion) of peramivir, it is necessary to identify usage conditions and collect safety information over a certain period of time, covering all patients treated with peramivir, in order to identify treated patients and usage conditions when peramivir has been made available to clinical practice, and take necessary action for the proper use of peramivir.

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

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

[Indication]
Influenza A or B virus infection

[Dosage and administration]
Usually, for adults, 300 mg of peramivir should be administered as a single intravenous infusion over at least 15 minutes.
For patients at high risk for severe influenza complications etc., 600 mg of peramivir should be administered as an intravenous infusion over at least 15 minutes. Once-daily multiple doses of 600 mg may be administered according to the patient's symptoms.
The dosage should be reduced, as appropriate, according to the patient's age and symptoms.

[Conditions for approval]
1. Collect post-marketing information on usage conditions and safety over a certain period of time, covering all patients treated with the product. Report the collected results to the regulatory authority periodically and take necessary action for the proper use of the product.
2. Report the results of Japanese and foreign surveillance of and information on peramivir-resistant influenza viruses to the regulatory authority, as required.