Report on the Deliberation Results

August 3, 2010
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Inavir Dry Powder Inhaler 20 mg
[Non-proprietary name]	Laninamivir Octanoate Hydrate (JAN*)
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	January 29, 2010

[Results of deliberation]
In the meeting held on July 29, 2010, 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, and 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.

**Japanese Accepted Name (modified INN)*

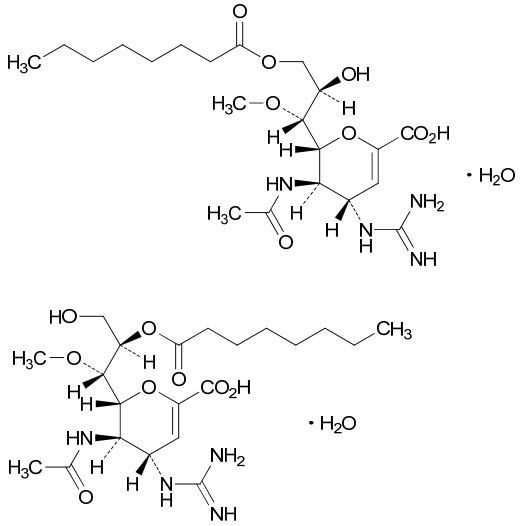
Review Report

July 7, 2010
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]	Inavir Dry Powder Inhaler 20 mg
[Non-proprietary name]	Laninamivir Octanoate Hydrate
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	January 29, 2010
[Dosage form/Strength]	Dry powder for inhalation: One inhaler contains 20.76 mg of Laninamivir Octanoate Hydrate (equivalent to 20 mg of laninamivir octanoate)
[Application classification]	Prescription drug- (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{21}H_{36}N_4O_8 \cdot H_2O$
Molecular weight: 490.55
Chemical name:

(2*R*,3*R*,4*S*)-3-Acetamido-4-guanidino-2-[(1*R*,2*R*)-2-hydroxy-1-methoxy-3-(octanoyloxy)propyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid monohydrate
(2*R*,3*R*,4*S*)-3-Acetamido-4-guanidino-2-[(1*S*,2*R*)-3-hydroxy-1-methoxy-2-(octanoyloxy)propyl]-3,4-dihydro-2*H*-pyran-6-carboxylic acid monohydrate

[Items warranting special mention]
None
[Reviewing office] Office of New Drug IV

Review Results

July 7, 2010

[Brand name]	Inavir Dry Powder Inhaler 20 mg
[Non-proprietary name]	Laninamivir Octanoate Hydrate
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	January 29, 2010

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with influenza A or B virus infection has been demonstrated, and the safety is acceptable in view of the observed benefits. Further investigations via post-marketing surveillance are needed on the efficacy of the product against each type/subtype of influenza virus such as subtype A/H3N2, type B, and novel subtype A/H1N1 as well as the safety in high-risk patients, which have not been sufficiently studied in the clinical studies of the product.

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

A prior assessment consultation was conducted on this product.

[Indication]
Treatment of influenza A or B virus infection

[Dosage and administration]

Adults:	Laninamivir octanoate 40 mg is administered by inhalation as a single dose.
Children aged <10 years:	Laninamivir octanoate 20 mg is administered by inhalation as a single dose.
Children aged ≥10 years:	Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

Review Report (1)

May 20, 2010

I. Product Submitted for Registration

[Brand name]	Inavir Dry Powder Inhaler 20 mg
[Non-proprietary name]	Laninamivir Octanoate Hydrate
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	January 29, 2010
[Dosage form/Strength]	Dry powder for inhalation: One inhaler contains 20.76 mg of Laninamivir Octanoate Hydrate (equivalent to 20 mg of laninamivir octanoate).
[Proposed indications]	Treatment of influenza A or B virus infection
[Proposed dosage and administration]	The usual dose for adults and children is 40 mg of laninamivir octanoate administered by inhalation in a single dose.

II. Summary of the Submitted Data and 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.

Laninamivir Octanoate Hydrate (hereinafter also referred to as "laninamivir octanoate"), which was discovered by Daiichi Sankyo Company, Limited, is a novel antiviral drug against influenza that selectively inhibits neuraminidase (NA) of influenza A or B virus. Similarly to existing NA inhibitors (oseltamivir phosphate, zanamivir hydrate), laninamivir octanoate is expected to prevent the growth of the virus by inhibiting NA and to improve influenza symptoms, leading to a shorter duration of illness.

Laninamivir octanoate is a prodrug of R-125489,[1] a compound that has NA-inhibitory activity. Results of nonclinical studies suggested that R-125489 is generally active in inhibiting NA of drug-resistant human influenza viruses reported with existing NA inhibitors. Also, R-125489 exhibited potent activity against animal influenza virus strains of all known NA subtypes. These results suggest that laninamivir octanoate may be an important option for the treatment of influenza in a situation involving a serious mutation, more specifically, a spread of a drug-resistant virus strain or an outbreak of pandemic influenza virus infection. The world experiences pandemics once every 10 years to several decades. In 2009, a pandemic of the H1N1 influenza virus was confirmed in the American Continent. Since 2003, human infection with highly pathogenic H5N1 avian influenza virus has been reported from many countries. Oseltamivir-resistant strains of the virus have been isolated from samples and are drawing attention of the international community. In this rapidly changing situation, the use of antiviral drugs is the only way to tackle influenza in the early stage of a pandemic, the need for which is growing from both medical and social points of view. Thus, the addition of a new treatment option is important.

Inavir Dry Powder Inhaler 20 mg ("Inavir") is administered by inhalation. Inhalation is expected to deliver a sufficient amount of drug to the target organs such as the airway immediately where

[1] R-125489, (2*R*,3*R*,4*S*)-3-Acetamido-2-[(1*R*,2*R*)–2,3-dihydroxy-1-methoxypropyl]-4-guanidino-3,4-dihydro-2*H*-pyran-6-carboxylic acid

viral growth occurs, thereby producing an efficient therapeutic effect. Since laninamivir octanoate is a prodrug designed to achieve increased retention at the infection site, the drug remains in the target organ for an extended period of time, resulting in the long-lasting therapeutic effect. Thus, whereas existing NA inhibitors need to be administered for 5 consecutive days, treatment with laninamivir octanoate is expected to complete with a single dose. This will increase drug compliance, and the drug is expected to decrease the shedding of the virus from the body while staying for an extended period of time in the target organ so that a spread of infection is contained.

The applicant explained that, based on the above discussion, laninamivir octanoate was developed to be a novel influenza antiviral drug with unique characteristics not shared by the existing drugs. [redacted].

As of May 2010, laninamivir octanoate has not been approved in foreign countries.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

[redacted].

(a) General properties

The determined physicochemical properties of the drug substance include description, solubility, hygroscopicity, thermal analysis, melting point (decomposition point), pH, partition coefficient, crystallinity, and crystalline polymorphism.

The drug substance is a white powder. It is freely soluble in dimethyl sulfoxide and in methanol, slightly soluble in ethanol (99.5), very slightly soluble in water, and practically insoluble in acetonitrile and in hexane. [redacted].

Under the condition of [redacted]°C/[redacted]% RH, a [redacted]% increase in the mass was observed after [redacted] hours, from which the drug substance was considered to be slightly hygroscopic. The pH of the saturated aqueous solution at 20°C was 5.8, and the partition coefficient ($LogP_{ow}$) in water/octanol system at 25°C was 0.0.

(b) Structure determination

The chemical structure of the drug substance is supported by elemental analysis, infrared spectrophotometry, nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR), and mass spectrometry. The drug substance has been confirmed to be a monohydrate by water content analysis, elemental analysis, solid NMR, and thermal analysis.

(c) Crystalline polymorphism

Presence of crystalline polymorphism has not been identified for the drug substance.

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

The Laninamivir Octanoate Hydrate drug substance is manufactured using Substance A as the starting material through the manufacturing processes comprising 4 steps. It is manufactured in Plant A located in Japan.

Step1: [redacted]

[redacted][2][redacted].

Step2: [redacted].

Step3: [redacted]. Substance produced is then dried under reduced pressure at [redacted]°C to obtain Laninamivir Octanoate Hydrate.

Step 4: Packaging process
Laninamivir Octanoate Hydrate is divided into small portions and packed in polyethylene bags, which are then packed in aluminum-foil bags and placed in drums.

(a) Controls of critical process steps and intermediates
The applicant stated that, in the manufacturing process of the drug substance, there were no processes or intermediates that had any critical effect on the quality of the drug substance.

(b) Manufacturing process development
[redacted].

2.A.(1).3) Control of drug substance
The specifications of the drug substance are established based on the measured values for the drug substance manufactured at the pilot scale (batch analyses), the stability studies, and the results of the validation of analytical methods.

[redacted].

(a) Reference standard
The proposed specifications for reference standard include description, identification (infrared spectrum, nuclear magnetic resonance spectrum [^{1}H]), purity (related substances, residual solvents), water content, residue on ignition, and purity.

(b) Container closure system
The drug substance is to be packed in low-density polyethylene bags, which are then packed and heat-sealed in aluminum-foil bags, and placed in steel drums.

[2] [redacted]

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

Long-term and accelerated studies of the drug substance were conducted using 3 pilot-scale batches each. Stress testing was conducted using one of these batches. The main storage conditions and storage period in each test are as shown below.

Long-term and accelerated studies

Study	Temperature	Humidity	Light	Storage form	Storage period
Long-term[a)]	5°C ± 3°C	Ambient	–	Low-density polyethylene bag/aluminum-foil bag/steel open drum	0, 3, 6, 9, 12 (at submission), 18, 24, 36, [redacted], [redacted], and [redacted] months
Accelerated	25°C ± 2°C	60% RH ± 5% RH	–	Same as above	0, 1, 3, 6 (at submission), [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] months

a) Additional data up to 24 months were submitted during the regulatory review.

Stress testing

Study		Temperature	Humidity	Light	Storage form	Storage period
Stress testing	Temperature	[redacted]°C ± [redacted]°C	[redacted]	–	[redacted]	0, [redacted], [redacted], and [redacted] weeks
		[redacted]°C ± [redacted]°C	[redacted]	–	Same as above	
	Temperature/ humidity	[redacted]°C ± [redacted]°C	[redacted]% RH ± [redacted]% RH	–	[redacted]	0, [redacted], [redacted], and [redacted] months
		[redacted]°C ± [redacted]°C	[redacted]% RH ± [redacted]% RH	–	Same as above	
		[redacted]°C ± [redacted]°C	[redacted]% RH ± [redacted]% RH	–	Same as above	
	Light	25°C ± [redacted]°C	60% RH ± [redacted]% RH	Under D65 fluorescent light	Glass Petri dish (open)	0, [redacted] × 10^4 lx·hr, [redacted] × 10^4 lx·hr, and 120 × 10^4 lx·hr (≥ 200W·h/m^2)

(a) Long-term and accelerated studies

In long-term studies, none of the test parameters showed over-time changes from baseline after 24 months of storage.

In accelerated studies, none of the test parameters showed over-time changes from baseline after 6 months of storage.

(b) Stress studies

In stress studies (temperature, temperature/humidity, light), none of the test parameters showed changes from baseline after the storage for the specified period.

Based on these results, a long-term retest period was proposed, according to "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003), to be 30 months, which is 6 months longer than the proven 24 months under refrigerated conditions. The retest period is planned to be extended depending on the results of the ongoing long-term testing.

2.A.(2) Drug product

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

The drug product is a dry powder for inhalation which contains Laninamivir Octanoate Hydrate (20 mg, on the anhydrous basis) filled in an inhaler (TwinCaps). The composition of the drug product is as shown below.

Components	Function	Content
Laninamivir Octanoate Hydrate (as laninamivir octanoate)	Active ingredient	20.76 mg (20 mg)
Lactose hydrate	Diluent	[redacted]
Total		[redacted] mg

(a) Pharmaceutical development

[redacted]. Prior to phase [redacted] studies, change of the inhaler was attempted and, based on the results of the clinical studies, TwinCaps were selected as the inhaler for commercial use. [redacted]. The formulations of the powder for the both drug products are reported to be identical.

[redacted].

(b) Formulation development

[redacted]. During the early stage of the development, Inhaler A was used as inhaler, and the amount of the fine particle dose[3] of the drug substance measured by an Andersen cascade impactor (ACI) was used as the index for selecting the formulation. [redacted].

Lactose hydrate was selected as diluent, based on the use experience in powder inhalers. [redacted].

[redacted]. In order to improve convenience, inhalers were re-studied and Inhaler A was then replaced by a disposable container TwinCaps. The formulation and manufacturing process of the drug product (dry powder) to be filled in TwinCaps are the same as those of the drug product for Inhaler A. The drug product (dry powder) containing 20 mg of laninamivir octanoate can be filled directly into 1 container. [redacted]

[3] The drug powder inhaled into the ACI reaches any one of 12 parts consisting of the ACI (mouthpiece adaptor, pre-separator, induction port, stages 0-7, filter), depending on the particle size. [redacted].

[redacted].

[redacted].

The change of Inhaler A to TwinCaps was studied in *in vitro* studies of inhalation characteristics and in clinical studies. Based on the results, it was determined that there were no problems in the use of TwinCaps as the commercial product [see "4.(i).B.(1) Comparison between Inhaler A and TwinCaps"].

2.A.(2).2 Manufacturing process

The drug product is produced through the manufacturing process comprising the following 6 steps and the manufacturing site will be Plant B located in Japan.

[redacted].

(a) Controls of critical process steps and intermediates

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

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

[redacted].

(a) Container closure system

The container closure system for the drug product is inhalers (TwinCaps) packed in an aluminum-foil bag. TwinCaps is a disposable inhaler developed for a single use, consisting of 2 parts, Body A and Body B, both of which are made of polypropylene. The Body B has 2 compartments to be filled with powder (dose compartments), and each compartment has a small air vent hole at the bottom. Sliding the Body B to one side allows the air vent hole of one of the dose compartments to align with another air vent hole at the bottom of the Body A so that an air passage is formed to allow the powder in the compartment to be inhaled.

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

Each of the main stability studies of the drug product submitted in this application was conducted using 3 batches manufactured at the pilot scale. The main storage methods and storage periods in the stability studies are as shown below.

[redacted]

[4] [redacted]

[redacted].

Long-term, accelerated, and intermediate studies

Study	Temperature	Humidity	Light	Form of storage	Storage period
Long-term[a)]	25°C ± 2°C	60% RH ± 5% RH	–	Inhalation container (TwinCaps)/ aluminum-foil bag	0, 3, 6, 9, 12 (at submission), 16, 24, 36, [redacted], [redacted], [redacted], and [redacted] months
Accelerated	40°C ± 2°C	75% RH ± 5% RH	–		0, 1, 3, and 6 (at submission) months
Intermediate[a)]	30°C ± 2°C	75% RH ± 5% RH	–		0, 1, 3, 6, 9, 12 (at submission), 16, and [redacted] months

a) Additional data up to 16 months were submitted during the regulatory review.

Stress studies

Study		Temperature	Humidity	Light	Form of storage	Storage period
Stress testing	Temperature	[redacted]°C ± [redacted]°C	[redacted]	–	Inhaler (TwinCaps) /aluminum-foil bag	0, [redacted], [redacted], and [redacted] weeks
		[redacted]°C ± [redacted]°C		–		
	Temperature /humidity	[redacted]°C ± [redacted]°C	[redacted]% RH ± [redacted]% RH	–	Inhaler (TwinCaps)	0, [redacted], [redacted], and [redacted] weeks
			[redacted]% RH ± [redacted]% RH	–		
			[redacted]% RH ± [redacted]% RH	–		0, [redacted], [redacted], and [redacted] hours, [redacted], [redacted], and [redacted] weeks
	Light	25°C ± [redacted]°C	45% RH ± [redacted]% RH	Under D65 fluorescent light	Glass Petri dish (open) or inhaler (TwinCaps)[a)]	0, [redacted] × 10^4 lx·hr, [redacted] × 10^4 lx·hr, and 120 × 10^4 lx·hr (≥ 200W·h/m^2)

a) The container closure system varied depending on the parameter tested.

In the long-term studies, none of the test parameters showed over-time changes for 16 months.

[redacted].

In the intermediate studies, none of the test parameters showed over-time changes for 16 months.

[redacted]. None of the other parameters showed over-time changes.

[redacted]. None of the other parameters showed over-time changes.

In the stress studies (light), none of the test parameters showed over-time changes.

Based on these results and according to the "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003), a proposed shelf life for the drug product when stored at room temperature is 16 months, the duration that the long-term testing so far has been performed. Since the long-term testing is ongoing, the shelf life is expected to be prolonged depending on the further results of the test.

2.B Outline of the review by PMDA

Based on the following reviews, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

2.B.(1) Manufacturing processes of the drug product

[redacted].

Since the specifications and the stability of lactose hydrate are considered to be important parameters to control the quality of the drug product, PMDA asked the applicant's view on these points (e.g., specifications and stability of the excipient, quality control measures).

The applicant responded as follows:

[redacted].

[redacted].

PMDA concluded that the inhalation characteristics of the drug product was to be controlled appropriately by the changes in the specifications of lactose hydrate, the key component, as mentioned in the response. PMDA also considers that there is no particular problem in the stability of lactose hydrate.

2.B.(2) Drug product specification

In order to control the inhalation characteristics of the drug product, fine particle dose (FPD) was included in the specifications of the drug product.

[redacted].

[redacted].

[redacted].

PMDA asked the applicant to reconsider the specifications for the FPD for the following reasons.

- While the applicant considers the appropriate dose of laninamivir octanoate is 40 mg rather than 20 mg from the clinical point of view [see "4.(ii).B.(3) Dosage and administration"], the acceptance criteria was defined based on the FPD achieved by the administration of 20 mg of laninamivir octanoate. The acceptance criteria should be re-defined based on the FPD at 40 mg of laninamivir octanoate to ensure the efficacy.

- FPD is an important quality attribute of the drug product. In order to keep manufacturing the product with consistent quality, the acceptance criteria must be defined with not only the lower limit but also the upper limit.

The applicant responded as follows:
The dose of 40 mg of laninamivir octanoate is considered more appropriate than 20 mg from the clinical point of view. Therefore, the acceptance criteria were re-examined based on the FPD following the administration of 40 mg of laninamivir octanoate. [redacted]. Toxicity studies fully ensured the safety of laninamivir octanoate and confirmed the appropriateness of the upper limit of the acceptance criteria [see "3.(iii).A Summary of the submitted data"].

Based on the above, the acceptance criteria for the FPD of the drug product is set at [redacted] to [redacted] mg.

PMDA accepted the applicant's response and concluded that the acceptance criteria for the FPD were re-defined appropriately.

2.B.(3) Stability studies on the drug product
Since the results of the long-term stability studies for the drug product showed relatively high over-time variability in water content, PMDA asked the applicant to explain the causative factors of the changes.

The applicant responded as follows:
A sample that had been stored under long-term storage conditions for 3 months was measured for water content to be compared with a starting sample as control that had been stored at room temperature. There was no difference in water content of the 3-month sample as compared with that measured at the start of the stability study ([redacted]%). Based on this result and the formulation attributes of the drug product, the high water content of the 3-month sample observed in the initial

testing was considered due to variability in measurements caused by the environmental factors. Since there were no operational errors in the measurement of water content of the 3-month sample, the initial high value ([redacted]%) was used as water content after 3-month storage.

In the light of the formulation attributes of the drug product, water content was considered not affected over time. The re-measurement of water content confirmed no over-time increase in water content in the 3-month sample. The applicant therefore considers that the changes in water content observed in the 3-month and 6-month samples in the long-term studies were due to variability in measurements caused by environmental factors, etc.

PMDA accepted the above response of the applicant. However, temperature and humidity after 3 months were not significantly different from those at the previous and next measuring time points. In order to eliminate contributory factors to variability in measurements, measuring conditions other than temperature and humidity should also be re-examined.

2.B.(4) [redacted]

[redacted][5] [redacted][6] [redacted].

[redacted].

[redacted]. Therefore, the applicant considered it more appropriate to use the test conditions under which secure inhalation would be ensured ("inhalation method employed with the commercial product") at that point.

In order to ensure the compliance of the drug product and secure inhalation by patients including children, the applicant plans to prepare and supply "guidance for patient instructions" and an "empty sample container (for demonstration)" to be used by healthcare professionals such as pharmacists for instructions on inhalation, "user manuals" to be supplied to patients together with the drug product, and "DVDs explaining the method for inhalation (for adults, for children)" to be used as supplementary material for dosing instructions. The "Precautions" section of the proposed package insert will include precautionary statements to the effect that "(2) the attached user manual should be handed over to the patient or his/her guardian. They should be instructed on how to use the product with a demonstration using the empty container" should be followed. The instruction materials for the inhalation technique to be used in clinical practice such as "guidance for patient instructions," "user manuals," and "DVDs explaining the method for inhalation (for adults, for children)" should illustrate the "inhalation method employed with the commercial product" including the technique of tapping on the bottom of the inhaler and other details of the inhalation procedure with an explanation on the importance of adherence to the procedure.

PMDA considers as follows:

[redacted]. Information on the methods for using the drug product, including those proposed in the applicant's response, should be appropriately provided to healthcare professionals in clinical practice to facilitate proper use of the drug product.

[redacted]

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

Results of 23 primary pharmacodynamic studies and 4 safety pharmacology studies as evaluation data and those of 4 primary pharmacodynamic studies as reference data were submitted for the application.

The dose of laninamivir octanoate is expressed on the anhydrous basis for primary pharmacodynamic studies and hERG studies, and on the hydrous basis for other safety pharmacology studies.

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

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

(a) Inhibition of human influenza virus NA (4.2.1.1-1 to 4.2.1.1-3)

Influenza A (H1N1, H2N2, H3N2)[7] or B virus[8] was used as enzyme source of NA to be mixed with each study drug, and enzyme activity was measured using a fluorescent substrate (4-methylumbelliferyl-*N*-acetyl-α-D-neuraminic acid [4MU-NANA]) to evaluate the NA-inhibitory effect (the concentration of the study drug required to inhibit 50 % of the enzyme activity [inhibitory concentration 50%, IC_{50}], where the enzyme activity in the absence of the study drug is assumed to be 100%) of each study drug. The IC_{50} values of R-125489, laninamivir octanoate, zanamivir, and the active form of oseltamivir phosphate (active form of oseltamivir) against NA of influenza A virus[9] were 2.32 to 38.8 nM, 0.0691 to 0.931 μM, 2.05 to 14.2 nM, and 0.925 to 3.44 nM, respectively. Those values against NA of influenza B virus[10] were 30.0 to 31.4 nM, 6.66 to 12.8 μM, 7.78 to 12.0 nM, and 12.0 to 15.6 nM, respectively.

Influenza A (H1N1, H3N2) or B virus strains (clinical isolates obtained during the period from 2002 through 2006) were used as enzyme source of NA to be mixed with each study drug, and the NA-inhibitory effect of each study drug was evaluated by measuring enzyme activity using 4MU-NANA. The results were as shown below.

Virus strain (subtype)	Number of strains	IC_{50}			
		R-125489 (nM)	Laninamivir octanoate (μM)	Zanamivir (nM)	Active form of oseltamivir (nM)
A (H1N1)	8	1.29-2.63	0.631-1.17	0.751-1.68	0.658-1.86
A (H3N2)	7	7.09-14.2	0.0392-0.131	3.42-7.58	0.706-1.09
B	18	10.4-26.5	3.50-45.5	3.55-7.59	3.09-13.7

Furthermore, oseltamivir-resistant strains and zanamivir-resistant strains isolated from patients with influenza virus infection were used as enzyme source of NA to be mixed with each study drug, and the NA-inhibitory effect of each study drug was evaluated by measuring enzyme activity using 4MU-NANA. The results were as shown below.

[7] Standard strain and vaccine strain
[8] Vaccine strain
[9] H1N1 type, 3 strains; H2N2 type, 1 strain; H3N2 type, 8 strains
[10] Type B, 5 strains

Virus strain (subtype)	Amino acid mutation [a)]	IC_{50} (nM)		
		R-125489	Zanamivir	Active form of oseltamivir
A/Yokohama/67/2006 clone-1 (H1N1)	WT	3.03	2.70	2.28
A/Yokohama/67/2006 clone-11 (H1N1)[b)]	H274Y	5.62	3.05	755
A/Kawasaki/IMS22A-954/2003 (H3N2)	WT	15.4	8.29	1.25
A/Kawasaki/IMS22B-955/2003 (H3N2)[b)]	R292K	10.6	11.2	10,400
A/Yokohama/IMS9A-2029/2003 (H3N2)	WT	19.2	10.7	1.78
A/Yokohama/IMS9B-2050/2003 (H3N2)[b)]	E119V	13.2	7.71	140
A/Kawasaki/MS31A-1030/2002 (H3N2)	WT	13.4	7.82	1.18
A/Kawasaki/MS31B-1206/2002 (H3N2)[b)]	N294S	37.3	13.5	37.2
B/Yokohama/UT2167/2005	WT	24.3	11.8	13.2
B/Yokohama/UT2175/2005[b)]	G402S	19.2	13.0	19.6
B/Yokohama/UT2203/2005[c)]	D198N	48.9	33.6	40.5
B/Yokohama/UT3318/2005[c)]	I222T	30.2	20.0	68.8
B/Yokohama/UT3081/2005[d)]	S250G	25.6	16.6	6.83

WT: Wild type

a) Amino acids are expressed in one-letter code. The amino acid number is expressed with reference to that in type N2 NA.

b) Oseltamivir-resistant strain

c) There is no corresponding wild type strain. It was reported to be resistant to oseltamivir.

d) There is no corresponding wild type strain. It was reported to be resistant to zanamivir.

(b) Inhibition of animal influenza virus NA (4.2.1.1-5)

Influenza H5N1 virus strains and influenza A virus strains of various NA subtypes (N3-N9) isolated from various animals were used as enzyme sources of NA to be mixed with each study drug, and the NA-inhibitory effect of each study drug was evaluated by measuring enzyme activity using 4MU-NANA. The IC_{50} values of R-125489, laninamivir octanoate, zanamivir, and the active form of oseltamivir were 1.81 to 27.9 nM, 0.142 to 1.14 μM, 1.40 to 11.5 nM, and 1.43 to 3.65 nM, respectively.

(c) Selectivity of NA-inhibitory effect (4.2.1.1-7)

R-125489 was mixed with NA of *Vibrio cholera*, *Clostridium perfringens*, or Newcastle disease virus and its NA-inhibitory effect was evaluated by measuring enzyme activity using 4MU-NANA. The IC_{50} values were >100 μM against NA of all bacterial and viral strains tested.

(d) Inhibitory effect on the proliferation of human influenza virus (4.2.1.1-8)

Influenza A (H1N1, H2N2, H3N2) or B virus strain was inoculated to Madin-Darby canine kidney (MDCK) cells and, after 1-hour infection, the cells were incubated for 30 to 45 hours on agar media containing each study drug. The cells were then stained in crystal violet to measure the inhibitory effect of each study drug against plaque formation (IC_{50}, the concentration of the study drug required to reduce 50 % of the number of plaques, where it is assumed to be 100% in the absence of the study drug) based on the number of plaques formed. The results were as shown below.

Virus strain	Subtype	IC_{50} (nM)			
		R-125489	Laninamivir octanoate	Zanamivir	Active form of oseltamivir
Standard strain					
A/Puerto Rico/8/34	H1N1	2.2	76	11	13
A/Singapore/1/57	H2N2	0.43	16	0.79	0.11
A/Aichi/2/68	H3N2	1.3	29	1.6	0.26
Vaccine strain					
A/Yamagata/32/89	H1N1	2.4	51	10	7.5
A/New Caledonia/20/99	H1N1	0.24	6.2	0.57	0.49
A/Kitakyushu/159/93	H3N2	1.7	45	3.3	0.37
A/Wyoming/03/2003	H3N2	230	>10,000	360	80
A/Wisconsin/67/2005	H3N2	2.7	43	2.1	0.95
B/Mie/1/93	B	4.2	110	9.2	21
B/Shanghai/361/2002	B	4.1	74	7.0	15
B/Brisbane/32/2002	B	5.8	100	6.4	28
B/Malaysia/2506/2004	B	9.9	200	22	120
B/Ohio/01/2005	B	11	150	15	42

(e) Inhibitory effect on the proliferation of animal influenza virus (4.2.1.1-9)

Either influenza H5N1 virus strains and NA of various subtypes (N3-N9) of influenza A virus strains isolated from various animals was inoculated to MDCK cells and, after 1-hour infection, the cells were incubated for 42 to 67 hours on agar media containing each study drug. The cells were then stained with crystal violet to measure the inhibitory effect of each study drug against plaque formation (IC_{50}). The IC_{50} values of R-125489, laninamivir octanoate, zanamivir, and the active form of oseltamivir were 0.26 to 2.5, 4.3 to 38, 0.58 to 3.6, and 0.093 to 0.88 nM, respectively.

(f) Cytotoxic effect (4.2.1.1-10)

Laninamivir octanoate or R-125489 (final concentration, 100 μg/mL)[11] was added to HeLa cells, MDCK cells (adhesive strain), and MOLT-4 cells (non-adhesive strain) to be incubated for 3 days. Then 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-*2H*-tetrazolium-5-carboxanilide sodium salt and phenazine methosulfate were added to the cells, which were incubated for an additional 1 hour to measure the absorbance (450 nm) for the evaluation of cytotoxic activity (CC_{50}, a concentration of the study drug required to reduce 50% of the absorbance, where it is assumed to be 100% in the absence of the study drug). The CC_{50} values of laninamivir octanoate and R-125489 were >100 μg/mL against all cells tested. The difference between CC_{50} and IC_{50} (the index of inhibitory effects against viral proliferation) of laninamivir octanoate was more than 1000-fold and that of R-125489 was more than several tens-of-thousands-fold.

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

(a) Antiviral effect against influenza A virus (post-infection administration) (4.2.1.1-11, 12, 17, 18)

Mice were infected intranasally with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 50 pfu) and, 24 hours after infection, received laninamivir octanoate (0.0014, 0.014, 0.15, 1.4 μmol/kg [equivalent to 0.66, 6.6, 71, and 660 μg/kg, respectively]), zanamivir (0.014, 0.15, 1.4, 14 μmol/kg [equivalent to 4.7, 50, 470, and 4700 μg/kg, respectively]), or control (vehicle) intranasally in a single dose. A homogenate of lung tissue of each mouse was infected with MDCK cells for 1 hour, and agar medium was added for incubation 2 to 4 days after infection. Pulmonary viral titers were measured by counting the number of plaques after 2-day incubation. Viral titers were significantly lower in the laninamivir octanoate group than in the zanamivir group, when they were administered at the same dose (0.15, 1.4 μmol/kg) (two-way analysis of variance using

[11] The final concentration of 100 μg/mL is equivalent to 210 μM for laninamivir octanoate and 290 μM for R-125489.

date of measurement and dose as explanatory variables; $P < 0.05$ at 0.15 μmol/kg, $P < 0.01$ at 1.4 μmol/kg). The percent area under the curve (the percentage of the area under the curve of the logarithmic values of pulmonary viral titers 2 to 4 days after infection relative to that in the control group) in the laninamivir octanoate and zanamivir groups were subjected to the covariance analysis using covariates including the dates of measurement, drugs, doses, and interactions of these covariates. The results showed a 3.64-fold greater antiviral effect in the laninamivir octanoate group than in the zanamivir group, but the difference was not statistically significant.

Mice were infected intranasally with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 50 pfu) and, 24 hours after infection, received laninamivir octanoate (0.015, 0.044, 0.13, 0.40 μmol/kg [equivalent to 7.1, 21, 61, and 190 μg/kg, respectively], zanamivir (0.15, 0.44, 1.3, 4.0 μmol/kg [equivalent to 50, 150, 430, and 1300 μg/kg, respectively]), or control (normal saline) intranasally in a single dose. The animals were then observed for survival up to 20 days after infection. A significant life-prolonging effect was observed at ≥0.044 μmol/kg (equivalent to 21 μg/kg) of laninamivir octanoate and at ≥1.3 μmol/kg (equivalent to 430 μg/kg) of zanamivir as compared with the control group (log-rank test, $P < 0.01$).

Mice were infected intranasally with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 30 pfu) and, at 11 hours after infection, received laninamivir octanoate (0.5 μmol/kg [equivalent to 240 μg/kg]) intranasally in a single dose, or twice daily (BID) for a maximum of 3 days, starting from 11 hours after infection. Separately, zanamivir (0.5 μmol/kg, the same dose as laninamivir octanoate [equivalent to 170 g/kg]) or control (normal saline) was administered to the animals in a single intranasal dose or repeated intranasal doses. Pulmonary viral titers were measured 35, 59, and 83 hours after infection. The least squares estimate of the logarithms of viral titers were compared between the single dose and repeated doses of laninamivir octanoate or between the single dose of laninamivir octanoate and the repeated doses of zanamivir by two-way analysis of variance. The results showed no significant difference in either of these comparisons.

Mice were infected intranasally with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 30 pfu) and, at 11 hours after infection, received laninamivir octanoate (0.057, 0.17 μmol/kg [equivalent to 27 and 80 μg/kg, respectively]) intranasally in a single dose. Separately, oseltamivir phosphate (1.0, 10 mg/kg) or control (normal saline) was administered to the animals orally BID for a maximum of 3 days, starting from 11 hours after infection. Pulmonary viral titers were measured 35, 59, and 83 hours after infection. The least squares estimate of the logarithms of viral titers were compared among the two dose groups of laninamivir octanoate and the oseltamivir phosphate 1.0 mg/kg group by two-way analysis of variance. The viral titers were significantly lower in the both laninamivir octanoate groups ($P < 0.01$).

(b) Antiviral effect against influenza A virus (pre-infection administration) (4.2.1.1-13 to 4.2.1.1-16)

Mice received laninamivir octanoate (0.18, 0.53, 1.6 μmol/kg [equivalent to 85, 250, and 760 μg/kg, respectively]), zanamivir (4.8, 14, 43 μmol/kg [equivalent to 1600, 4700, and 14,000 μg/kg, respectively]), or control (vehicle) intranasally in a single dose 7 days before intranasal infection with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 500 pfu). Pulmonary viral titers were measured 1, 2, 3, and 4 days after infection. Pulmonary viral titers were significantly lower in the laninamivir octanoate and zanamivir groups at all doses as compared with those in the control group (two-way analysis of variance using date of measurement and dose as explanatory variables, $P < 0.01$). The percent area under the curve (the percentage of the area under the curve of the logarithmic values of pulmonary viral titers 1 to 4 days after infection relative to that in the control group) in the laninamivir octanoate group and those in the zanamivir group were subjected to covariance analysis using dose as covariate. The results showed a 32.8-fold greater antiviral effect in the laninamivir octanoate group than in the zanamivir group, showing a statistically significant difference ($P < 0.01$).

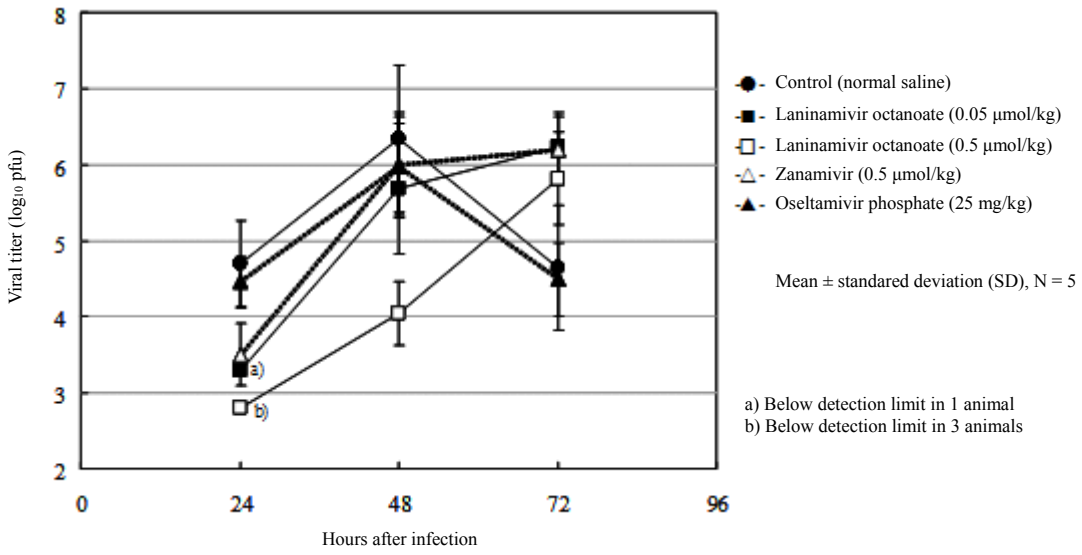
Mice received laninamivir octanoate (0.20, 0.39, 0.78, 1.5 μmol/kg [equivalent to 95, 180, 370, and 710 μg/kg, respectively]), zanamivir (5.2, 10, 21, 42 μmol/kg [equivalent to 1700, 3300, 7000, and 14,000 μg/kg, respectively]), or control (normal saline) intranasally in a single dose 7 days before intranasal infection with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 500 pfu) and were observed for survival up to 20 days after infection. A significant life-prolonging effect was observed at ≥0.78 μmol/kg of laninamivir octanoate and at all doses except 10 μmol/kg of zanamivir, as compared with the control group. (log-rank test, $P < 0.01$ [$P < 0.05$ at 5.2 μmol/kg of zanamivir]).

Mice received laninamivir octanoate (0.5 μmol/kg [equivalent to 240 μg/kg]), zanamivir (0.5 μmol/kg [equivalent to 170 μg/kg]), or control (normal saline) intranasally in a single dose 1, 4, 7, 10, or 14 days before intranasal infection with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 500 pfu) and were observed for survival up to 20 days after infection. A significant life-prolonging effect was observed as compared with the control group in animals receiving laninamivir octanoate 1, 4, 7, 10 days before infection and in animals receiving zanamivir 1 day before infection only (log-rank test, $P < 0.01$ [$P < 0.05$ in animals receiving zanamivir 1 day before infection and in animals receiving laninamivir octanoate at 10 days before infection]). A statistically significant life-prolonging effect was observed in animals receiving laninamivir octanoate 1, 4, 7, 10 days before infection as compared with the zanamivir group, (log-rank test, $P < 0.01$ [$P < 0.05$ in animals receiving laninamivir octanoate at 1 day before infection]).

Mice received a single intranasal dose of laninamivir octanoate (0.037, 0.37, 1.5 μmol/kg [equivalent to 17, 170, and 710 μg/kg, respectively]), a single oral dose of oseltamivir phosphate (1.1, 11, 110 mg/kg), or a single intranasal or oral dose of control (normal saline) 12 hours or 1, 4, or 7 days before intranasal infection with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 100 pfu) and were observed for survival up to 20 days after infection. In the laninamivir octanoate groups, a significant life-prolonging effect was observed as compared with the control group, at all doses administered 1 day before infection and at ≥0.37 μmol/kg administered 12 hours, 4 days, or 7 days before infection (log-rank test, $P < 0.01$ [$P < 0.05$ in the 0.37 μmol/kg group receiving laninamivir octanoate 7 days before infection]). In contrast, in the oseltamivir phosphate groups, a significant life-prolonging effect was observed only in the 110 mg/kg group receiving the drug 12 hours or 1 day before infection (log-rank test; $P < 0.01$ in administration 12 hours before infection, $P < 0.05$ in administration at 1 day before infection).

(c) Antiviral effect against influenza B virus (post- and pre-infection administration) (4.2.1.1-22 to 4.2.1.1-23)

Ferrets were infected with influenza B/Malaysia/2506/2004 virus (inoculation dose, 1200 pfu) intranasally and, 4 hours after infection, received laninamivir octanoate (0.05, 0.5 μmol/kg [equivalent to 24 and 240 μg/kg, respectively]), zanamivir (0.5 μmol/kg [equivalent to 170 μg/kg]), or control (normal saline) intranasally in a single dose or oseltamivir phosphate (25 mg/kg BID) orally for 3 days. Viral titers in nasal lavage fluid were measured 24, 48, and 72 hours after infection. The results were as shown in the following figure.



Decrease in viral titers in nasal lavage fluid induced by laninamivir octanoate or zanamivir (single intranasal dose) or by oseltamivir phosphate (BID, repeated oral dose for 3 days)

Mice received laninamivir octanoate (0.16, 0.49, 1.5 μmol/kg [equivalent to 76, 230, and 710 μg/kg, respectively]), zanamivir (3.3, 9.8, 29 μmol/kg [equivalent to 1100, 3300, and 9600 μg/kg, respectively]), or control (normal saline) intranasally in a single dose 7 days before intranasal infection with influenza B/Hong Kong/5/72 virus (inoculation dose, 1500 pfu) and were observed for survival up to 20 days after infection. A significant life-prolonging effect was observed in the laninamivir octanoate groups at ≥0.49 μmol/kg and in the zanamivir groups at all doses as compared with the control group (log-rank test, $P < 0.01$ [$P < 0.05$ at 3.3 μmo1/kg of zanamivir]).

(d) Antiviral effect by inhalation (pre-infection administration) (4.2.1.1-24 to 4.2.1.1-25)
Mice received laninamivir octanoate (0.24, 0.91 nmol/lungs) or control (air) by inhalation in a single dose[12], or laninamivir octanoate (0.30, 0.60, 1.2, 2.0, 4.0 nmol/body) or control (normal saline) intranasally in a single dose[13] 2 days before intranasal infection with influenza A/PR/8/34 (H1N1) virus (inoculum dose, 500 pfu) and were observed for survival up to 20 days after infection. All animals (8 of 8 animals) in the control group (inhalation, intranasal dose) died on or before 9 days after infection. In the laninamivir octanoate inhalation group, 7 of 8 animals receiving 0.24 nmol/lungs and all animals (8 of 8 animals) receiving 0.91 nmol/lungs survived 20 days after infection. In the laninamivir octanoate intranasal dose group, 4 of 8 animals receiving 0.30 nmol/body, 7 of 8 animals receiving 0.60 nmol/body, and all animals (8 of 8 animals) receiving 1.2 nmol/body survived 20 days after infection. The applicant stated that the result suggested that laninamivir octanoate had the life-prolonging effect by inhalation as was observed with an intranasal dose.

3.(i).A.(1).3) Study on pandemic influenza A virus (H1N1) (Reference data, 4.2.1.1-4)
Published literature on the effect of antiviral drugs on a pandemic influenza A (H1N1) virus, which outbreak was confirmed in the American Continent in April 2009 (hereinafter referred to as "pandemic influenza A [H1N1] virus") (*Nature*. 2009;460(7258):1021-1025) was submitted as reference data.

[12] The dose indicates the drug concentration in the lungs immediately after administration (sum of laninamivir and R-125489).
[13] Calculated from the drug concentration and the volume of the dosing solution

The IC_{50} values of R-125489 against the pandemic influenza A (H1N1) virus strains, A/California/04/09 and A/Osaka/164/09, were 0.41 and 0.44 nM, respectively; those of zanamivir were 0.32 and 0.43 nM, respectively; and those of the active form of oseltamivir were 0.96 and 1.6 nM, respectively.

The IC_{90} (concentration of the drug required to reduce 90% of the viral titer) value of R-125489 against the pandemic influenza A (H1N1) virus strain, A/California/04/09, was 4.24 nM; that of zanamivir was 17.67 nM; and that of the active form of oseltamivir was 10.56 nM.

Mice were infected intranasally with the pandemic influenza (H1N1) virus (A/California/04/09; inoculum dose, 10,000 pfu) and, 1 hour after infection, received laninamivir octanoate (700 μg/kg) intranasally in a single dose, zanamivir (0.8, 8 mg/kg/day) intranasally once daily (QD) for 5 days, or oseltamivir phosphate (8, 80 mg/kg/day BID) orally for 5 days. Viral titers in the lungs was measured 3 and 6 days after infection. Viral titers in the laninamivir octanoate group were significantly lower as compared with the control groups (t-test; $P < 0.01$ at 3 days after infection, $P < 0.05$ at 6 days after infection).

3.(i).A.(1).4) Study on highly pathogenic avian influenza (H5N1) virus (Reference data, 4.2.1.1-6)

Published literature on the effect of antiviral drugs against a highly pathogenic avian influenza (H5N1) virus (*PLoS Pathog*. 2010 Feb 26;6(2)) was submitted as reference data.

The IC_{50} values of study drugs against highly pathogenic avian influenza (H5N1) virus strains isolated from infected patients were as shown below.

Virus strain	Amino acid mutation (clone No.)	IC_{50} (nM)		
		R-125489	Zanamivir	Active form of oseltamivir
A/Hanoi/30408/05	Wild type (Clone 7)[1)]	0.32	0.72	0.35
	H274Y (Clone 9)[2)]	1.1	0.68	430
	N294S (Clone 3)[2)]	1.6	0.57	1.6
A/Vietnam/1203/04	Wild type[1)]	0.28	0.15	0.31
	H274Y[2)]	2.1	0.22	1100
	N294S[2)]	1.4	0.48	28
A/Indonesia/UT3006/05	Wild type[1)]	0.29	0.07	10

1) Oseltamivir-sensitive strain, 2) Oseltamivir-resistant strain

Mice were infected intranasally with a highly pathogenic avian influenza (HPAI) H5N1 virus strain, A/Hanoi/30408/05 (clone 7) or A/Indonesia/UT3006/05 (inoculation dose, 4 times the 50% lethal dose in mice [MLD_{50}]), and received either laninamivir octanoate (75, 750, 1500 μg/kg) or control (normal saline) intranasally in a single dose 2 hours after infection, or either oseltamivir phosphate (5, 50 mg/kg) or control (distilled water) orally BID for 5 days. Lung and brain viral titers were measured 3, 6, and 9 days after infection. In animals infected with any virus strain, laninamivir octanoate at 75 μg/kg decreased the lung viral titers until 3 days after infection, and laninamivir octanoate at ≥750 μg/kg decreased the lung viral titers until 6 days after infection while maintaining the brain viral titers below the detection limit until 9 days after infection. In animals infected with the HPAI H5N1 A/Hanoi/30408/05 (clone 7), oseltamivir phosphate at 50 mg/kg decreased the lung viral titer while maintaining the brain viral titer below the detection limit until 6 days after infection. In animals infected with the HPAI H5N1 A/Indonesia/UT3006/05, oseltamivir phosphate did not exhibit clear decrease in the lung viral titers at either doses tested.

Mice were infected intranasally with a highly pathogenic avian influenza H5N1 virus strain,

A/Vietnam/1203/04, A/Vietnam/1203/04-H274Y, or A/Vietnam/1203/04-N294S (inoculum dose, MLD_{50}). The animals received either laninamivir octanoate (75, 750, 1500 μg/kg) or control (normal saline) intranasally in a single dose 2 hours after infection, or either oseltamivir phosphate (5, 50 mg/kg) or control (distilled water) orally BID for 5 days and were observed for survival up to 21 days after infection. In the control groups with any viral strains, all animals died on or before 14 days after infection. In animals infected with the HPAI H5N1 A/Vietnam/1203/04, the numbers of surviving animals 21 days after infection in the laninamivir octanoate 75, 750, and 1500 μg/kg groups were 1 of 8, 4 of 8, and 7 of 8, respectively, and those in the oseltamivir phosphate 5 and 50 mg/kg groups were 3 of 8 and 6 of 8, respectively. In animals infected with the HPAI H5N1 A/Vietnam/1203/04-H274Y, the numbers of surviving animals 21 days after infection in the laninamivir octanoate 75, 750, and 1500 μg/kg groups were 4 of 8, 7 of 8, and 8 of 8, respectively, and those in the oseltamivir phosphate 5 and 50 mg/kg groups were 1 of 8 and 4 of 8, respectively. In animals infected with the HPAI H5N1 A/Vietnam/1203/04-N294S, the numbers of surviving animals 21 days after infection in the laninamivir octanoate 75, 750, and 1500 μg/kg groups were 0 of 10, 6 of 10, and 8 of 10, respectively, and in the oseltamivir phosphate 5 and 50 mg/kg groups were 1 of 10 and 5 of 10, respectively.

3.(i).A.(1).5) Study on influenza virus resistance (Reference data, 4.2.1.1-26)

Mice were infected intranasally with the influenza A/PR/8/34 (H1N1) virus (inoculum dose, 30 pfu) and treated with either laninamivir octanoate ([redacted] μg/kg) intranasally in a single dose 9 hours after infection or oseltamivir phosphate ([redacted] mg/kg) orally BID for 5 days. A total of [redacted] virus strains were isolated from the lung homogenates of mice treated with laninamivir octanoate, and [redacted] virus strains from those treated with oseltamivir phosphate [redacted] days after infection by plaque assay to measure NA-inhibitory activities (IC_{50}). No resistant virus strains were isolated from the mice treated with laninamivir octanoate, whereas [redacted] strains with amino acid mutations (amino acid mutations [redacted]) with reduced susceptibility to oseltamivir phosphate were isolated from mice treated with the drug. Of these [redacted] strains, one strain ([redacted]) showed cross-resistance to laninamivir octanoate (IC_{50} ratio[14], [redacted]).

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

No data on secondary pharmacodynamics were submitted in the present application.

3.(i).A.(3) Safety pharmacology (4.2.1.3-1 to 4.2.1.3-4)

Data from 4 safety pharmacology studies were submitted in the present application. The main outline and results of the studies are as shown below.

[14] Ratio of IC_{50} for mutant strain versus wild-type strain

Test item		Animal (sex)	Route of administration	Dose (mg/kg)	N	Results
Central nervous system	General conditions/behaviors	Mice (male)	Inhalation	Laninamivir octanoate: 0.9, 6.1, 69.7	3	0.9, 6.1 mg/kg: No effect 69.7 mg/kg*: Increased alertness (2/3 animals), increased response to pain (2/3), abnormal posture (crouching) (2/3), abnormal gait (tiptoe walking) (2/3), slight increase in exploratory behavior (3/3), aggressive behavior (2/3)
	Motor function	Mice (male)	Inhalation	Laninamivir octanoate: 0.7, 9.0, 85.6	6	Static activity: Slight effect at 0.7, 9.0, 85.6 mg/kg[b)] (transient), dose-independent Mobile and rearing activity: No effect Mobile time: No effect
	Motor coordination	Mice (male)	Inhalation	Laninamivir octanoate: 0.7, 9.0, 85.6	6	No effect
	Duration of hexobarbital anesthesia	Mice (male)	Inhalation	Laninamivir octanoate: 0.9, 6.1, 69.7	6	No effect
Cardiovascular system	Systolic blood pressure Diastolic blood pressure Mean blood pressure Heart rate ECG	Rats [a)] (male)	Intratracheal	Laninamivir octanoate: 3, 10, 30	4	Systolic blood pressure: No effect Diastolic blood pressure: No effect Mean blood pressure: No effect Heart rate: Transient decrease at 30 mg/kg [b)] ECG: No effect
	Isolated atrium Beat rate of (right atrium, automatic rhythm) Contractile force (left atrium, electric rhythm)	Guinea pigs (male)	*in vitro*	Laninamivir octanoate: 0.3, 1, 3 (μg/mL) R-125489: 0.3, 1, 3 (μg/mL)	8	Heart rate: No effect Myocardial contractile force: No effect
	hERG current	hERG-introduced CHO cells	*in vitro*	Laninamivir octanoate: 3, 10, 30 (μmol/L) R-125489: 3, 10, 30 (μmol/L)	5[c)]	No effect
Respiratory system	Respiratory rate Tidal volume Minute ventilation volume	Rats (male)	Intratracheal	Laninamivir octanoate: 3, 10, 30	4	Respiratory rate: No effect Tidal volume: No effect Minute ventilation volume: No effect
Gastrointestinal system	Intestinal motility	Mice (male)	Inhalation	Laninamivir octanoate: 0.7, 9.0, 85.6	6	No effect
Renal/urological system	Urine output Urine specific gravity Urine osmolality Sodium, potassium, chlorine, calcium, phosphorus Total protein Urine creatinine Creatinine clearance	Rats (male)	Inhalation	Laninamivir octanoate: 1.4, 9.2, 84.3	6	Urine output: No effect Urine specific gravity: No effect Urine osmolality: No effect Sodium, potassium, chlorine, calcium: No effect Phosphorus: Slight increase at 84.3 mg/kg [b)] Total protein: No effect Urine creatinine: No effect Creatinine clearance: No effect

a) Evaluation under urethane anesthesia; b) $P < 0.05$ (vs. control group, Dunnett test); c) Cell count/group

* [Note by PMDA: Even in the control group, increased alertness, increased exploratory behavior, and aggressive behavior were observed in 1 of 3 animals each. Among them, the increased exploratory behavior and the aggressive behavior had been observed since before administration].

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

3.(i).B.(1) Inhibitory effect against NA of strains isolated in clinical studies

PMDA asked the applicant to explain the antiviral activity of laninamivir octanoate against strains isolated in clinical studies of the drug product.

The applicant responded as follows:

For the purpose of submission of regulatory application for laninamivir octanoate, a total of 8 clinical studies were conducted from 2007 through 2009 in patients with influenza virus infection. Clinical isolates obtained from participants in these studies were subjected to a test for NA-inhibitory activity of R-125489 and the active form of oseltamivir, and the following results were obtained. In either season, no viral strains with high IC_{50} of R-125489 were isolated.

NA-inhibitory activity (IC_{50}) of R-125489 and the active form of oseltamivir against strains isolated in clinical studies conducted in the 2007/2008 season (A/H1N1 subtype, A/H3N2 subtype, type B)

Active form	Viral type	No of subjects with identified viral type	No. of evaluable subjects	IC_{50} (nM)					
				Arithmetic mean	SD	Geometric mean	Median	Minimum	Maximum
R-125489	A/H1N1 subtype	362	333	1.355	0.372	1.303	1.400	0.54	2.50
	A/H3N2 subtype	70	63	2.749	0.541	2.700	2.700	1.80	4.30
	Type B	39	35	17.657	3.842	17.278	17.000	12.00	29.00
Active form of oseltamivir	A/H1N1 subtype	362	333	11.908	86.972	1.192	0.970	0.25	770.00
	A/H3N2 subtype	70	63	0.733	0.119	0.722	0.730	0.37	0.99
	Type B	39	35	14.546	2.771	14.274	15.000	8.20	21.00

Study designs: Phase II single dose study, Taiwanese phase II study

NA-inhibitory activity (IC_{50}) of R-125489 and the active form of oseltamivir against strains isolated in clinical studies conducted in the 2008/2009 season (A/H1N1 subtype, A/H3N2 subtype, type B)

Active form	Viral type	No of subjects with identified viral type	No. of evaluable subjects	IC_{50} (nM)					
				Arithmetic mean	SD	Geometric mean	Median	Minimum	Maximum
R-125489	A/H1N1 subtype	1082	955	1.802	0.609	1.700	1.800	0.45	4.40
	A/H3N2 subtype	509	462	2.312	0.577	2.240	2.300	0.78	4.40
	Type B	70	69	18.610	4.087	18.106	19.000	9.00	26.00
Active form of oseltamivir	A/H1N1 subtype	1082	955	673.297	229.848	626.668	690.000	89.00	1500.00
	A/H3N2 subtype	509	462	0.686	0.150	0.669	0.685	0.27	1.40
	Type B	70	69	22.638	7.302	21.768	20.000	12.00	53.00

Study designs: Phase II multiple dose study, global phase III study, comparative study on inhalers, study in patients aged ≤9 years, study in teenage patients, PK study in pediatric subjects

PMDA considers the antiviral effect of laninamivir octanoate as follows:

a) Influenza A virus

Based on the response of the applicant, PMDA confirmed that the IC_{50} values of R-125489 against virus strains in the 2007/2008 season were similar to those against influenza A/H1N1 virus in the 2008/2009 season, during which a pandemic of the virus with H274Y mutation occurred.[15]

[15] Infectious Agents Surveillance Report (IASR) of Infectious Disease Surveillance Center: Information on the detection of seasonal influenza (A/H1N1) virus strains resistant to oseltamivir in the 2008/2009 season (http://idsc.nih.go.jp/iasr/rapid/pr3503.html)

PMDA also confirmed that the IC_{50} values of R-125489 against influenza A/H3N2 virus were similar between the 2007/2008 and 2008/2009 seasons.

Taking account of the submitted data and the response of the applicant, laninamivir octanoate is expected to be effective against influenza A virus. However, some of the virus strains investigated showed higher IC_{50} values of R-125489 than those of other antiviral drugs against influenza [see "3.(i).A.(1).1).(a) Inhibition of human influenza virus NA"]. Therefore, further information on the resistance to R-125489 should be collected.

(b) Influenza B virus

Based on the response of the applicant, PMDA confirmed that IC_{50} values of R-125489 against influenza B virus in the 2007/2008 season were similar to those in the 2008/2009 season. According to the submitted data and the response of the applicant, the NA-inhibitory activity (IC_{50}) of R-125489 against influenza B virus was higher than that against influenza A virus. However, laninamivir octanoate is expected to be effective against influenza B virus, based on the following findings: (a) NA-inhibitory activity (IC_{50}) of laninamivir octanoate against influenza B virus is not significantly different from that of existing influenza antiviral drugs (active form of oseltamivir, zanamivir), and (b) in the *in vivo* study in ferrets, the viral titer was apparently reduced 24 hours after infection in the laninamivir octanoate group as compared with the placebo group [see "3.(i).A.(1).2).(c) Antiviral effect against influenza B virus"].

However, in the study in ferrets, the viral titer in the laninamivir octanoate group was higher 72 hours after infection as compared with the control group.

The applicant explained these findings as follows:

The decrease in the viral titer in the nasal lavage fluid in the control group 72 hours after infection was due to a decrease in the number of uninfected cells in the nasal cavity as a result of viral infection, thereby limiting further growth of the virus. In the laninamivir octanoate group, in contrast, non-infected cells remained even 72 hours after infection because of the drug's inhibitory effect against the proliferation of the virus. An increased number of viral particles collected from the nasal lavage fluid resulted in a higher viral titer as compared with the control group.

PMDA considers that, while the applicant's explanation is understandable, it is unclear whether or not the dosage regimen (single-dose administration) investigated is effective enough.

A final conclusion on the clinical efficacy of laninamivir octanoate for the treatment of influenza A and B virus infections should be made by taking account of the results of clinical studies [see "4.(ii).B.(1) Efficacy"].

3.(i).B.(2) Cross-resistance between laninamivir octanoate and other influenza antiviral drugs (NA inhibitors)

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

The applicant responded as follows:

The resistance mechanism of seasonal H1N1 virus with H274Y mutation, one of oseltamivir-resistant virus strains, was reported (*Nature.* 2008;453(7199):1258-1261). According to the report, a hydrophobic group (pentyloxy group) of the active form of oseltamivir keeps a distance from the carboxyl group of Glu276 in NA and forms a hydrophobic interaction with methylene moiety of Glu. On the other hand, in zanamivir, the glycerol moiety interacts with the carboxyl group of Glu276 in NA, similarly to sialic acid. When mutation of His to Tyr occurs at position 274 in NA in the active form of oseltamivir, Try pushes the carboxyl group of Glu276 into the binding site of the NA inhibitor so that the pentyloxy group in the active form of oseltamivir is shifted, thereby

the binding force to NA is reduced. In zanamivir, however, since the interaction between the glycerol moiety and Glu276 is not blocked by the mutation, the drug maintains the inhibitory activity against oseltamivir-resistant virus with H274Y mutation. In R-125489, the methoxy group at position 1 is equivalent to the glycerol group in zanamivir and, since the methoxy group is unlikely to interact with NA, R-125489 also is considered to maintain the activity against the virus with H274Y mutation by the similar mechanism similar to zanamivir.

Data of the *in vitro* antiviral activity of R-125489 against oseltamivir-resistant virus isolated from patients with influenza infection [see Tables in "3.(i).A.(1).1).(a) Inhibition of human influenza virus NA"] shows that there were no oseltamivir-resistant virus strains[16] against which the inhibitory activity of the drug decreased substantially as compared with the wild-type strain. These results suggest that known clinically isolated oseltamivir-resistant virus strains have little or no cross-resistance to R-125489.

Among type B virus strains reported to be zanamivir-resistant, the S250G-mutated strain was shown to be highly sensitive to NA inhibition by R-125489. The R152K-mutated strain was unavailable and was not tested for sensitivity to R-125489.

PMDA accepted the explanation of the applicant that laninamivir octanoate is unlikely to have cross-resistance to oseltamivir-resistant virus strains due to its chemical structure. On the other hand, cross-resistance of laninamivir octanoate to zanamivir-resistant strains have not been documented by sufficient data because of the limited number of strains investigated. Therefore, the possibility of cross-resistance between laninamivir octanoate and other antiviral drugs against influenza cannot be excluded, and the use of laninamivir octanoate may pose a risk of the emergence of a resistant virus strain. Further information on the viral resistance to laninamivir octanoate should be collected.

3.(i).B.(3) Efficacy of laninamivir octanoate against pandemic influenza A (H1N1) virus and highly pathogenic avian influenza (H5N1) virus

Based on the published literature that was submitted, PMDA considers that R-125489 is expected to have an antiviral activity against the pandemic influenza A (H1N1) virus and highly pathogenic avian influenza (H5N1) virus. However, since clinical efficacy is unknown at present, further relevant information should be collected.

3.(i).B.(4) Safety pharmacology

PMDA asked the applicant to discuss the changes suggestive of an effect on the central nervous system observed in the safety pharmacology studies in mice.

The applicant responded as follows:

The safety pharmacology study in mice showed the following changes suggestive of an effect on the central nervous system: increased alertness, increased response to pain, and abnormal gait until 2 hours after administration (2 of 3 animals) and aggressive behavior until 4 hours after administration (2 of 3 animals), all in the laninamivir octanoate hydrate 69.7 mg/kg group. However, since these changes were not statistically significant and similar changes were observed in the control group as well,[17] a causal relationship between the central nervous system symptoms and the use of laninamivir octanoate hydrate is unclear. No data were available on systemic exposure to laninamivir octanoate after inhalation to mice, precluding the accurate calculation of the safety range of the exposure levels. However, the dose level in mice at which the changes were observed was approximately 8.3 times higher than the recommended clinical dose, when

[16] Except 2 influenza B virus strains without corresponding wild-type strain (B/Yokohama/UT2203/2005, B/Yokohama/UT3318/2005)

[17] Increased alertness and aggressive behavior up to 4 hours after administration (1 of 3 animals each), increased exploratory behavior up to 2 hours after administration (1 of 3 animals)

compared on a mg/m^2 basis. The level of laninamivir octanoate distributed in the central nervous system was extremely limited [see "3.(ii).A.(2) Distribution"]. These results suggest that laninamivir octanoate is unlikely to affect the central nervous system at the recommended clinical dose.

Precautions regarding the risks of psychiatric disorder/neurologic symptoms such as abnormal behaviors after the administration of laninamivir octanoate are to be included in the package insert, as are the cases with the similar drugs.

PMDA considers as follows:
In the safety pharmacology study, a similar effect on the central nervous system was observed in the control group as well. However, increased exploratory and aggressive behaviors had already been observed since before administration. In the laninamivir octanoate hyderate 69.7 mg/kg group, on the other hand, the only event that had been observed before administration was increased exploratory behavior (1 of 3 animals), and all other events were observed only after administration. Therefore, it is difficult to completely rule out the possible effect of laninamivir octanoate on the central nervous system at this point. Given only the limited level of laninamivir octanoate is distributed in the central nervous system, the conduct of an additional non-clinical study is not necessary at this stage. However, relevant information should be collected continuously from published reports, etc. The results of clinical studies should be taken into account when finalizing specific ways to provide cautions against the effect on the central nervous system [see "4.(ii).B.(2) Safety"].

3.(ii) Summary of pharmacokinetic studies

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

^{14}C-labeled or unlabeled laninamivir octanoate or its active metabolite R-125489 was administered intratracheally, intranasally, intravenously, or orally to mice, rats, and dogs to investigate the pharmacokinetics of the drug. Note that the dose of laninamivir octanoate is expressed on the anhydrous basis in this report.

The concentrations of laninamivir octanoate and R-125489 in the biological samples were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS), and the radioactivity of ^{14}C-labeled laninamivir octanoate and R-125489 in the biological samples were measured by a liquid scintillation counter (LSC). Tissue distribution of radioactivity was investigated by whole-body autoradiography. Unchanged laninamivir octanoate and metabolites in the biological samples treated with ^{14}C-labeled laninamivir octanoate were measured by an imaging analyzer after being separated by thin-layer chromatography (TLC). In some studies, radio-high performance liquid chromatography (Radio-HPLC) was used to investigate the percentage of each metabolite relative to the total radioactivity.

3.(ii).A.(1) Absorption (4.2.2.2-1 to 4.2.2.2-10)

Laninamivir octanoate (0.1, 0.2, 0.4 mg/kg in rats; 0.2 mg/kg in dogs) was administered intratracheally in a single dose to rats and dogs. Plasma pharmacokinetic parameter values were as shown in the table below. Because C_{max} (maximum plasma concentration) and AUC_{last} (area under the plasma concentration-time curve up to the last quantifiable time point) of laninamivir octanoate and R-125489 in rats increased generally in a dose-proportional manner, the pharmacokinetics of laninamivir octanoate was considered generally linear over the dose range tested (0.1-0.4 mg/kg). In a separate study, ^{14}C-labeled laninamivir octanoate (0.2 mg/kg) was administered intratracheally in a single dose to rats and dogs to investigate changes in blood or plasma radioactivity concentrations. Radioactivity reached C_{max} 0.7 to 0.88 hours after

administration in both animals (rats, 86 ng eq./mL [plasma]; dogs, 77 ng eq./mL [blood], 120 ng eq./mL [plasma]) and was then eliminated gradually.[18]

Plasma pharmacokinetic parameters following a single intratracheal dose of laninamivir octanoate to rats and dogs

	Dose (mg/kg)	Analyte	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{last} (ng·h/mL)
Rats	0.1	Laninamivir octanoate	0.7	52.9	0.8	104
	0.2		0.5	74.6	0.8	152
	0.4		0.6	143	0.9	330
	0.1	R-125489	1.0	7.03	3.0	29.6
	0.2		1.0	12.2	11.6	81.7
	0.4		2.0	21.0	14.1	219
Dogs	0.2	Laninamivir octanoate	0.8	62.4	2.0	216
		R-125489	3.0	10.7	42.9[a)]	127

Mean (n = 4 [n = 2 for a)])
t_{max}: Time to maximum plasma concentration

Laninamivir octanoate (0.4 mg/kg) was administered intratracheally to rats to calculate bioavailability based on AUC[19] values following a single intravenous dose of laninamivir octanoate or R-125489 (0.4 mg/kg each). The bioavailabilities of laninamivir octanoate and R-125489 were 52.1% and 30.1%, respectively. The bioavailabilities of laninamivir octanoate and R-125489 following oral administration of laninamivir octanoate (0.4 mg/kg) to rats were 0.3% and 3.5%, respectively.

Laninamivir octanoate (0.4 mg/kg) was administered intratracheally in a single dose to rats to compare $t_{1/2}$ (elimination half-life in the terminal phase, 14.1 hours) with $t_{1/2}$ following a single intravenous dose of R-125489 (0.4 mg/kg) or laninamivir octanoate (0.4 mg/kg). The $t_{1/2}$ of intratracheal laninamivir octanoate was longer than that of R-125489 following the single intravenous dose of R-125489 (0.4 mg/kg) (0.5 hours) and was comparable to that of R-125489 following a single intravenous dose of laninamivir octanoate (0.4 mg/kg) (10.6 hours).

3.(ii).A.(2) Distribution (4.2.2.3-1 to 4.2.2.3-10)

^{14}C-labeled laninamivir octanoate, ^{14}C-labeled R-125489, and ^{14}C-labeled zanamivir (0.5 μmol/kg each [equivalent to 240 μg/kg of laninamivir octanoate, 173 μg/kg of R-125489, and 170 μg/kg of zanamivir, respectively]) was administered intranasally in a single dose to mice. Radioactivity remained in the nasal cavity, trachea, and lung for a longer period after administration of ^{14}C-labeled laninamivir octanoate than after administration of ^{14}C-labeled R-125489 or zanamivir. In a separate study, laninamivir octanoate (0.5 μmol/kg) was administered intranasally in a single dose to mice. Laninamivir octanoate concentration in the lungs rapidly decreased, with $t_{1/2}$ being 0.833 hours, whereas R-125489 concentration in the lungs gradually decreased, with $t_{1/2}$ being 41.4 hours. In still another study, laninamivir octanoate or zanamivir (0.5 μmol/kg each) was administered intranasally in a single dose, or twice daily for 3 days, to mice infected with influenza A virus. R-125489 concentration in the lungs was higher than the concentration of laninamivir octanoate or zanamivir in the lungs (15-29 fold in single-dose administration, 15-20 fold in repeat-dose administration).

^{14}C-labeled laninamivir octanoate (0.4 mg/kg) was administered intratracheally in a single dose to rats. High radioactivity was detected in the trachea, lungs, liver, and kidney 15 minutes after administration and was remarkable especially in the lungs while little or no radioactivity was

[18] $t_{1/2}$ was 4.74 hours (plasma) in rats and 25.3 hours (blood) and 28.8 hours (plasma) in dogs.
[19] $AUC_{0\text{-}inf}$ (area under plasma concentration-time curve from time 0 to infinity) of laninamivir octanoate, 637 ng·h/mL; AUC_{last} of R-125489, 993 ng·h/mL

distributed in the central nervous system (brain, spinal cord) or in the testis 24 and 72 hours after administration. Following a single intratracheal dose of ^{14}C-labeled laninamivir octanoate (0.2 mg/kg), high radioactivity was observed primarily in the lungs and the trachea until 0.5 hours after administration, whereas 1 hour after administration and later, it was higher in the trachea, lungs, liver, and kidney than the blood radioactivity concentration. In contrast, radioactivity concentrations in the tissue of other organs were similar to or lower than that in plasma, and in the cerebrum and the cerebellum were lower than in plasma[20] and were not detected 24 hours after administration and later. Radioactivity in the lungs was eliminated only gradually ($t_{1/2}$, 23.2 hours) and 8.56% of the total administered radioactivity still remained 48 hours after administration.

^{14}C-labeled laninamivir octanoate or ^{14}C-labeled R-125489 (0.4 mg/kg each) was administered intravenously in a single dose to pregnant rats on Gestation day 13 or 18. Radioactivity was detected in the uterus, ovary, placenta, and amniotic membrane at a concentration similar to or lower than the blood radioactivity concentration 0.5 hours after administration. In the amniotic membrane, radioactivity was detected even 24 hours after administration (rats on Gestation day 13) or 48 hours after administration (rats on Gestation day 18). Extremely low level of radioactivity was detected in fetuses 0.5 hours after administration in rats on Gestation day 13 and 0.5 and 6 hours after administration in rats on Gestation day 18. Following administration of ^{14}C-labeled R-125489 to rats on Gestation day 18, radioactivity was detected in the liver and bladder urine of fetuses, whereas radioactivity levels in tissue of other organs were below the detection limit.

In male rats, male dogs, and male humans, *in vitro* plasma protein binding rates of ^{14}C-labeled laninamivir octanoate and R-125489 (2, 5, 20 μg/mL and 0.2, 2, 20 μg/mL, respectively) were 57.1% to 69.9% and ≤2.1%, respectively, in any species. *In vitro* distributions in blood cells of ^{14}C-labeled laninamivir octanoate and R-125489 (2, 5, 20 μg/mL and 0.2, 2, 20 μg/mL, respectively) were as low as ≤5.0% and ≤3.4%, respectively, in any species. Similarly, after ^{14}C-labeled laninamivir octanoate (0.2 mg/kg) was administered intratracheally in a single dose to dogs, most blood radioactivity was present in plasma, suggesting low distributions in blood cells.

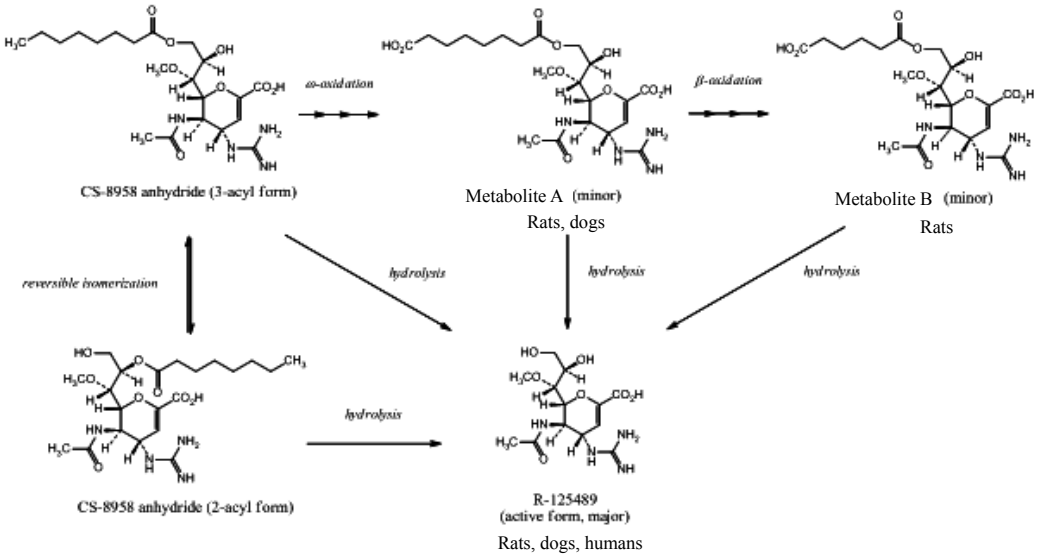
3.(ii).A.(3) Metabolism (4.2.2.4-1 to 4.2.2.4-14)

Following a single intratracheal dose of ^{14}C-labeled laninamivir octanoate (0.3 mg/kg) to rats, R-125489 was detected as metabolite in plasma, as well as in the trachea and lungs. In contrast, following a single intravenous dose of ^{14}C-labeled laninamivir octanoate (10 mg/kg) to rats, a slight amount of a metabolite with an oxidized alkyl side chain (Metabolite A) was observed in the plasma and urine, in addition to the main metabolite R-125489, and another metabolite, a β-oxidized form of Metabolite A (Metabolite B), was detected in bile. Following the intratracheal dose of ^{14}C-labeled laninamivir octanoate (0.3 mg/kg) to dogs, R-125489 was observed in the lungs and plasma, R-125489 and Metabolite A were observed in urine, and Metabolite A was observed in bile.

In vitro metabolic studies were conducted using the S9 fractions of the lungs of female mice, male rats, male dogs, and humans, and airway epithelial cell lysates of rats and humans (EGV-4T cells, NHBE cells). In all animal species studied, R-125489 was detected as metabolite, and the amount of the metabolite increased with time up to 60 minutes. Interindividual variability in the hydrolysis of laninamivir octanoate was investigated using human lung S9 fraction. The hydrolysis rates were 3.41 to 8.75 pmol/min/mg protein (n = 10), showing no significant interindividual variability and suggesting little or no effect of a smoking habit or sex.

[20] Kp of radioactivity in the cerebrum and in the cerebellum (concentration ratio between brain versus plasma) was low, at approximately 0.1 at the maximum.

The possible metabolic pathway of laninamivir octanoate in rats, dogs, and humans is as shown in the following figure.



Possible metabolic pathway of laninamivir octanoate in rats, dogs, and humans

Effects of inhibitors (DFP, BNPP, eserine, DTNB)[21] on the hydrolysis of laninamivir octanoate were investigated using human lung S9 fraction (samples pooled from 4 non-smoking men and 2 non-smoking women). Hydrolysis of laninamivir octanoate was inhibited strongly by DFP, to some extent by high concentration of BNPP and DTNB, but little by eserine, which suggested possible involvement of multiple enzymes such as serine hydroxylases (e.g., carboxylesterase) and thiol group-containing hydroxylases in the hydrolysis of laninamivir octanoate.

3.(ii).A.(4) Excretion (4.2.2.5-1 to 4.2.2.5-5)

Following a single intratracheal dose of ^{14}C-labeled laninamivir octanoate (0.2 mg/kg) to rats and dogs, the cumulative excretion rates of radioactivity into urine and feces up to 72 hours (rats) or 96 hours (dogs) after administration were approximately 90%. The excretion rates into urine and feces up to 168 hours after administration were 67.52% and 29.55%, respectively, in rats and 76.52% and 18.31%, respectively, in dogs, which showed that laninamivir octanoate was excreted mainly into urine. The biliary excretion rate of radioactivity in rats up to 48 hours after administration was 16.06%. Following a single intravenous dose of ^{14}C-labeled laninamivir octanoate (0.2 mg/kg) to rats, the excretion rates of radioactivity in urine and feces up to 168 hours after administration were 63.07% and 36.41%, respectively. Following a single intravenous dose of ^{14}C-labeled R-125489 (0.2 mg/kg), the excretion rates of radioactivity in urine and feces up to 168 hours after administration were 88.89% and 8.25%, respectively.

Following a single intravenous dose of ^{14}C-labeled laninamivir octanoate or ^{14}C-labeled R-125489 (0.4 mg/kg each) to nursing rats, radioactivity was detected in milk in the both groups. Radioactivity levels in milk were higher than in plasma 2 hours after administration and later. Following the administration of ^{14}C-labeled laninamivir octanoate, the radioactivity in milk was eliminated as rapidly as that in plasma, whereas following the administration of ^{14}C-labeled R-125489, the radioactivity was eliminated more gradually in milk than in plasma.

[21] DFP: Diisopropylfluorophosphate, BNPP: bis(4-nitrophenyl) phosphate, DTNB: 5,5'-Dithiobis(2-nitrobenzoic acid)

3.(ii).A.(5) Pharmacokinetic drug interactions (4.2.2.6-1, 4.2.2.6-2)

Results of *in vitro* CYP inhibition studies showed that neither laninamivir octanoate nor R-125489 of the concentration range tested (final concentration, 0.03-30 μM) (IC_{50} > 30 μM) inhibited cytochrome P450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) in the human liver. In *in vitro* CYP induction studies, the activity of laninamivir octanoate and R-125489 to induce human liver cytochrome P450 isoforms (CYP1A2, CYP3A4) was investigated using, as positive controls, omeprazole (CYP1A2) and rifampicin (CYP3A4). As a result, neither laninamivir octanoate nor R-125489 at the concentrations tested (0.1, 1, 10 μM) induced the enzymes.[22]

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

3.(ii).B.(1) Retention of R-125489 in the lung

PMDA asked the applicant to explain how long R-125489 can be maintained at the concentration high enough to exert its effect in the lungs after intratracheal or intranasal administration of laninamivir octanoate.

The applicant responded as follows:

In the pharmacology study using a mouse model of influenza A virus (A/PR/8/34) infection, laninamivir octanoate (0.5 μmol/kg) was administered intranasally in a single dose 11 hours after viral infection. Laninamivir octanoate significantly decreased viral titer as compared with the control (normal saline) [see "3.(i).A.(1).2).(a) Antiviral effect against influenza A virus (post-infection administration)"]. Also, laninamivir octanoate showed a significant life-prolonging effect as compared with the control group (normal saline) following a single intranasal dose of 0.5 μmol/kg at 10 days before viral infection [see "3.(i).A.(1).2).(b) Antiviral effect against influenza A virus (pre-infection administration)"]. On the other hand, after laninamivir octanoate (0.5 μmol/kg) was administered intranasally in a single dose to mice in a pharmacokinetic study (4.2.2.3-6), $t_{1/2}$ of R-125489 in the lungs was as long as 41.4 hours, demonstrating that R-125489 remains in the lungs for an extended period. Also, the concentration of R-125489 in the lungs 5 days after administration, the last measuring time point, was 317 ng/g lung (0.915 nmol/g), which is equivalent to 1100 nM, assuming that the volume of 1 g of lung is 0.83 mL.[23] This concentration is ≥100 times the IC_{50} (5.97 nM) of R-125489 against influenza A virus (A/PR/8/34). Based on these results, the applicant considers that R-125489 remains at a high concentration that allows almost complete inhibition of the release of a virus from the host cells for at least 5 days after the administration of laninamivir octanoate.

PMDA considers as follows:

Half-life ($t_{1/2}$) of R-125489 in the lungs was 41.4 hours after the administration of a single intranasal dose of laninamivir octanoate (0.5 μmol/kg) to mice. The R-125489 concentration in the lungs at 5 days after administration exceeded the IC_{50} (5.97 nM) of R-125489 against influenza A virus (A/PR/8/34). Because of these findings, R-125489 is expected to remain in the lungs for an extended period and its concentration remains high enough to exert the drug effect against influenza A virus (A/PR/8/34) even at 5 days after administration of laninamivir octanoate. On the other hand, no discussion was made on influenza B virus. Although the data showed that the IC_{50} of R-125489 against influenza B virus (maximum value reported in the submitted data, 26.5 nM) is higher as compared with that against influenza A virus [see "3.(i).B.(1) Inhibitory effect against NA of strains isolated in clinical studies"], the R-125489 concentration in the lungs at 5 days after administration of laninamivir octanoate in mice exceeds the above IC_{50}, suggesting that

---

[22] According to some reports on induction of major P450 isoforms other than CYP1A2 and CYP3A4, drugs that do not induce CYP3A4 do not induce CYP2C8, CYP2C9, or CYP2C19 either, CYP2D6 induction has never been reported and there are no known drugs that clinically induce CYP2D6 (Center for Drug Evaluation and Research [CDER], Center for Biologics Evaluation and Research [CBER]. Guidance for industry: drug interaction studies-study design, data analysis, and implications for dosing and labeling [DRAFT GUIDANCE], September 2006, *AAPS J*. 2008;10:391-400).

[23] *Pharm Res*. 1993;10:1093-1095.

the R-125489 concentration in the lungs remains, for a certain period, high enough to exert its therapeutic effect against influenza B virus as well as against influenza A virus. The results of clinical studies should be taken into account when the final decision is made on the clinical efficacy of laninamivir octanoate against influenza A and B viruses.

3.(ii).B.(2) Differences between genders and between juvenile and mature animals

3.(ii).B.(2).1) Gender-related differences

PMDA asked the applicant to explain gender differences in the pharmacokinetics of laninamivir octanoate.

The applicant responded as follows:

In the 2- and 4-week repeat-dose inhalation toxicity studies in rats, plasma TK parameters C_{max} and $AUC_{0\text{-}t}$ of laninamivir octanoate and R-125489 did not show any marked differences between male and female rats on Day 1 of the administration of laninamivir octanoate (maximum dose, possible maximum dose). Also, little or no difference was observed in TK parameters between male and female rats at all doses other than the maximum dose, or at the last day of administration (Day 15 or 28). These results suggest that there are no clear gender-related differences in the pharmacokinetics of laninamivir octanoate. No gender-related differences were observed in TK parameters in dogs either.

PMDA considers the applicant's conclusion that there are no clear gender-related differences in the pharmacokinetics of laninamivir octanoate is not appropriate because of the following findings on the TK study data: (a) gender differences were observed in the pharmacokinetic parameters (C_{max}, $AUC_{0\text{-}22h}$, $AUC_{0\text{-}23h}$, $AUC_{0\text{-}24h}$) of laninamivir octanoate and R-125489 at non-maximum doses of laninamivir octanoate in male and female rats, and (b) gender-related differences were observed in male and female dogs as well. Since no consistent trend was observed in these gender-related differences in the pharmacokinetics of laninamivir octanoate, making a decision on whether or not there are gender-related differences in the pharmacokinetics of laninamivir octanoate is difficult based on these data. Therefore, PMDA asked the applicant to discuss gender-related differences based on the data of clinical studies.

The applicant responded as follows:

Plasma concentrations of laninamivir octanoate and R-125489 by gender in the phase III study to compare the inhalers (study to compare inhalers, Study CS8958-A-J304) and in the phase I study in pediatric patients (≤ 15 years of age) with influenza virus infection (pediatric PK study, Study CS8958-A-J204) were as shown in the following table. In the multiple dose group in the study to compare inhalers (Study CS8958-A-J304) and in the pediatric PK study (Study CS8958-A-J204), TK parameter values tended to be higher in female subjects than in male subjects, whereas in the single-dose group in the pediatric PK study (Study CS8958-A-J204), the values tended to be higher in male subjects than in female subjects. However, because of the large interindividual variability both in male and female subjects, no clear gender-related difference was confirmed. Also, in the PPK analysis (5.3.3.5-1), gender was not selected as significant covariant for F1, distribution volume, clearances included in the final model. Therefore, there is no gender-related difference in the pharmacokinetics of laninamivir octanoate or R-125489.

Plasma concentrations of laninamivir octanoate and R-125489 in male and female subjects in the study to compare inhalation containers (Study CS8958-A-J304)

Blood sampling time	Analyte	Plasma concentration (ng/mL)	
		Male (N = 18)	Female (N = 14)
1 hr after administration	Laninamivir octanoate	141.441 ± 63.994	155.065 ± 43.476
	R-125489	14.566 ± 6.891	16.614 ± 6.804
4 hr after administration	Laninamivir octanoate	62.231 ± 28.939	70.521 ± 14.609
	R-125489	26.182 ± 12.073	28.824 ± 9.046
120 hr after administration	Laninamivir octanoate	0.000 ± 0.000	0.000 ± 0.000
	R-125489	2.184 ± 0.943	2.562 ± 1.334

Mean ± SD

Plasma concentrations of laninamivir octanoate and R-125489 in males and females in pediatric PK study (Study CS8958-A-J204)

Blood sampling time	Analyte	Plasma concentration (ng/mL)	
		Male (N = 18)	Female (N = 14)
1 hr after administration	Laninamivir octanoate	195.551 ± 70.867	194.917 ± 122.051
	R-125489	22.502 ± 7.844	22.893 ± 15.390
4 hr after administration	Laninamivir octanoate	79.482 ± 25.086	59.852 ± 37.993
	R-125489	35.956 ± 12.352	31.317 ± 17.231
24 hr after administration	Laninamivir octanoate	1.200 ± 1.134	0.968 ± 0.984
	R-125489	10.844 ± 3.374	9.201 ± 4.857
144 hr after administration	Laninamivir octanoate	0.000 ± 0.000	0.000 ± 0.000
	R-125489	1.665 ± 1.233	1.558 ± 1.538

Mean ± SD

Taking account of the above clinical study data, PMDA accepted the applicant's explanation that there are no clear gender-related differences in the pharmacokinetics of laninamivir octanoate and R-125489.

3.(ii).B.(2).2) Difference between juvenile and mature animals

PMDA asked the applicant to explain the difference in the pharmacokinetics of laninamivir octanoate between juvenile and mature animals.

The applicant responded as follows:

A 4-week repeat-dose inhalation toxicity study in juvenile rats (administration started at 27 days of age) and in mature rats (administration started at 8-10 weeks of age in males and at 10-12 weeks of age in females) was conducted. No marked differences were observed between juvenile and mature rats in plasma TK parameters of C_{max}/Dose and $AUC_{0\text{-}23h}$/Dose (C_{max} and $AUC_{0\text{-}23h}$ adjusted for dose) of laninamivir octanoate or R-125489 on Day 1 of the administration of laninamivir octanoate. The applicant therefore considers that there are no clear differences in the pharmacokinetics of laninamivir octanoate by age.

Based on the evaluation of the plasma TK parameters at each time point in the 4-week repeat-dose inhalation toxicity study in rats, PMDA accepted the applicant's view that there are no clear differences in the pharmacokinetics of laninamivir octanoate by age.

3.(ii).B.(3) Blood-brain transfer in juvenile animals

PMDA asked the applicant to discuss the transfer of laninamivir octanoate into the brain in juvenile animals.

The applicant responded as follows:

Generally, the blood-brain barrier controls the passage of substances into the brain by efflux transporters such as P-glycoprotein (P-gp) and through intercellular gaps. P-gp expression in the cerebral blood vessels is known to be less frequent in juvenile rats than in mature rats. Oseltamivir,

which is a drug similar to laninamivir octanoate, serves as substrate for P-gp and is reported to be transferred into the brain at higher rate in juvenile rats than in mature rats (*Drug Metab Dispos*. 2008;36:427-434). In order to verify whether or not laninamivir octanoate and its active metabolite R-125489 serve as substrates for P-gp, transcellular transport of these compounds was investigated using cells expressing human P-gp (hMDR1) (data of a preliminary study). The ratio of the membrane permeability coefficient in the basal-to-apical direction to that in the apical-to-basal direction (P_{app}, ratio) was greater in hMDR1-expressing cells (MDCK-MDR1) than in the control cells (MDCK-parent) with oseltamivir, whereas P_{app}, ratio was ≤ 1 with ^{14}C-labeled laninamivir octanoate, ^{14}C-labeled R-125489, and the active form of oseltamivir (Ro64-0802), showing that they do not serve as substrates for hMDR1. These results suggest that the blood-brain transfer of laninamivir octanoate is primarily due to passive diffusion and therefore no change occurs in blood-brain transfer attributable to an age-related difference in P-gp expression level. Also, a report on comparable rates of blood-brain transfer of mannitol in juvenile rats (1 week of age) mature rats (*Brain Res Dev Brain Res*. 1995;87:69-76) suggests that blood-brain transfer of substances through intercellular gaps are controlled in juvenile rats as is the case with mature rats. Furthermore, the TK data of 4-week repeat-dose inhalation toxicity studies in juvenile rats and mature rats indicate that the exposure level of laninamivir octanoate is unlikely to become extremely high in juvenile rats as compared with mature rats [see "3.(ii).B.(2).2) Difference between juvenile and mature animals"]. Based on these findings, the applicant considers that there is no extreme difference in the blood-brain transfer of laninamivir octanoate between juvenile and mature animals.

PMDA considers as follows:
The applicant's explanation on no extreme difference in the blood-brain transfer of laninamivir octanoate between juvenile and mature animals is understandable, given the observations (a) that the study on the transcellular transport using human P-gp (hMDR1)-expressing cells suggested that laninamivir octanoate and R-125489 do not serve as substrates for P-gp (hMDR1) and therefore the difference in P-gp expression levels between juvenile and mature rats is unlikely to affect the blood-brain transfer of laninamivir octanoate, (b) that the study using mannitol suggests that the rates of blood-brain transfer through intercellular gaps does not differ between juvenile and mature rats, and (c) that the TK data did not show any marked difference in the pharmacokinetic parameters between juvenile and mature rats. On the other hand, the safety pharmacology study in mice [see "3.(i).A.(3) Safety pharmacology"] revealed changes suggestive of an effect of laninamivir octanoate on the central nervous system (e.g., increased exploratory behavior, aggressive behavior). Therefore, the presence of an effect of laninamivir octanoate on the central nervous system cannot be completely ruled out at present and should be determined in a comprehensive manner based on the results of clinical studies.

3.(ii).B.(4) Drugs that affect the hydrolysis of laninamivir octanoate
PMDA asked the applicant to explain whether or not precautions should be provided on the concomitant use of drugs affecting the hydrolysis of laninamivir octanoate to its active metabolite R-125489 in clinical settings.

The applicant responded as follows:
Multiple enzymes in the body including carboxylesterase are thought to be involved in the hydrolysis of laninamivir octanoate to R-125489 (4.2.2.4-14). The result of the study on the concentration dependency of hydrolysis using human lung S9 fraction (4.2.2.4-13) showed that the hydrolysis rate of laninamivir octanoate increases with the concentration of the drug, suggesting that even a high concentration (1000 μM) of the drug cab be hydrolyzed in the lung S9 fraction. Therefore, multiple enzymes are assumed to be involved in the hydrolysis of laninamivir octanoate. As long as these enzymes exhibit sufficient metabolic activities, hydrolysis is unlikely to be affected by drug interaction. The applicant presumes there is no drug that could

affect the hydrolysis of laninamivir octanoate significantly in routine clinical use. Therefore, the provision of precautions on the use of concomitant drugs in clinical settings is not necessary.

PMDA accepted the applicant's response that since multiple enzymes are thought to be involved in the hydrolysis of laninamivir octanoate to R-125489, the hydrolysis is unlikely to be affected by the interaction of laninamivir octanoate with concomitant drugs and therefore the provision of precautions on the use of concomitant drugs in clinical setting is not necessary.

3.(iii) Summary of toxicology studies

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

The toxicological profile of laninamivir octanoate was investigated in single-dose and repeat-dose toxicity studies (including juvenile animals), genotoxicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (antigenicity studies).

The dose and concentration of laninamivir octanoate is expressed on the anhydrous basis in the 4-week repeat-dose toxicity studies (rats, juvenile rats, dogs) and on the hydrated basis in other studies. In inhalation studies, the drug substance or a substance generated from the mixed powder of laninamivir octanoate and lactose hydrate prepared according to the clinical formulation (content of drug substance, 20%) was inhaled via an aerosol container for 1 hour (2 hours in the reproductive and developmental toxicity studies) once daily, and the dose was estimated from the concentration in the aerosol, inhalation time, minute ventilation volume, and body weight.

3.(iii).A.(1) Single-dose toxicity study (4.2.3.1-1 to 4.2.3.1-7)

The following single-dose toxicity studies were conducted using the maximum possible concentration (dose): inhalation studies in rats (including juvenile animals) and dogs (4.2.3.1-1, 4.2.3.1-7, 4.2.3.1-2) and intravenous administration studies in mice and rats (4.2.3.1-3, 4.2.3.1-4). The approximate lethal dose was determined to be >178.6 mg/kg in male and female rats, >105 mg/kg in male and female juvenile rats, >40.2 mg/kg in male dogs, >39.6 mg/kg in female dogs in inhalation; and >125 mg/kg in both male and female mice and rats in intravenous administration. Intravenous administration studies of R-125489, the active metabolite of laninamivir octanoate, was conducted in mice and rats (4.2.3.1-5, 4.2.3.1-6), and the approximate lethal dose was determined to be >70 mg/kg in males and females of both animal species. No abnormality was observed in clinical signs, body weight, pathological tests (necropsy only in rodents), etc., after administration in any of these studies.

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

Repeat-dose toxicity was evaluated by repeat-dose inhalation studies in rats (2 and 4 weeks), juvenile rats (4 weeks), and dogs (2 and 4 weeks). The drug substance was used in the 2-week studies, and the mixed powder of laninamivir octanoate and lactose hydrate prepared according to the clinical formulation (content of drug substance, 20%) was used in the 4-week studies. No toxicologically significant changes were observed following the administration of laninamivir octanoate in any of the studies. A comparison of the no observed adverse effect level (NOAEL) of laninamivir octanoate in the 4-week studies (5.8 mg/kg/day in rats, 5.76 mg/kg/day in dogs; both were the maximum possible dose) and the exposures to the active metabolite R-125489 following a single dose inhalation of laninamivir octanoate 40 mg in Japanese healthy adult male subjects (phase I single dose study [Study CS8958-A-J102]) showed safety margins of C_{max} of approximately 6-fold (rats) and approximately 20 fold (dogs), and of AUC^{24} of approximately 2 fold (rats) and approximately 7 to 8 fold (dogs). There were neither qualitative nor quantitative differences in the toxicity observed in juvenile animals as compared with that in mature animals.

[24] The comparison was made using $AUC_{0\text{-}23h}$ in rats and dogs, and using $AUC_{0\text{-}24h}$ in humans.

3.(iii).A.(2).1) Two-week inhalation study in rats (4.2.3.2-1)

Laninamivir octanoate (0 [air], 21.6, 45.4, 84.9 mg/kg/day [maximum possible concentration]) was administered by inhalation for 14 or 16 days to male and female rats (9-12 weeks of age). Changes observed were increased mean corpuscular volume in the ≥45.4 mg/kg groups, decreased red blood cell count and increased mean cell hemoglobin in the 84.9 mg/kg group. The changes observed in the 84.9 mg/kg group persisted even after the 14-day withdrawal period, but all were slight changes and considered to be of no toxicological significance. Histopathological examination showed a slight increase in the number of alveolar macrophages in all groups receiving laninamivir octanoate, but the change was not correlated with dose and returned to the level comparable to the historical data after the withdrawal period. The change was therefore considered to be nonspecific physiological response to the inhalation. The NOAEL in this study was determined to be 84.9 mg/kg/day, the maximum possible dose.

3.(iii).A.(2).2) Four-week inhalation study in rats (4.2.3.2-3)

Laninamivir octanoate (0 [air], 0 [vehicle, lactose hydrate], 0.67, 2.1, and 5.8 mg/kg/day [maximum possible dose]) was administered by inhalation for 28 days (male) or 29 days (female) to male and female rats (8-12 weeks of age). As compared with the vehicle control group, decreased food intake and increased lactic dehydrogenase in the ≥2.1 mg/kg groups, decreased mean cell hemoglobin concentration, increased reticulocyte count, increased white blood cell count, increased neutrophil count, increased basophil count, increased lymphocyte count, decreased glucose, increased sodium, and increased inorganic phosphorus in the 5.8 mg/kg group were observed. These changes were not observed after the 28-day withdrawal period and were slight even when compared with the air control group. The changes were considered to have no toxicological significance. The NOAEL in this study was determined to be 5.8 mg/kg/day, the maximum possible dose.

3.(iii).A.(2).3) Four-week inhalation study in juvenile rats (4.2.3.2-5)

Laninamivir octanoate (0 [air], 0 [vehicle, lactose hydrate], 0.69, 2.6, 9.1 mg/kg/day [maximum possible dose]) was administered by inhalation for 28 days (male) or 29 days (female) to male and female juvenile rats (27 days of age). As compared with the vehicle control group, increased plasma sodium and chlorine were observed in the ≥0.69 mg/kg groups. However the changes were minor and not accompanied by any pathological changes and therefore were considered to have no toxicological significance. The NOAEL in this study was determined to be 9.1 mg/kg/day, the maximum possible dose.

3.(iii).A.(2).4) Two-week inhalation study in dogs (4.2.3.2-2)

Laninamivir octanoate (0 [air], 3.66, 10.81, 38.1 mg/kg/day) was administered by inhalation for 15 days (males) or 16 days (females) to male and female beagle dogs. Laninamivir octanoate had no effect, from which the NOAEL was determined to be 38.1 mg/kg/day.

3.(iii).A.(2).5) Four-week inhalation study in dogs (4.2.3.2-4)

Laninamivir octanoate (0 [vehicle, lactose hydrate], 0.58, 1.92, 5.76 mg/kg/day [maximum possible dose]) was administered by inhalation for 28 days to male and female beagle dogs. Increased fibrinogen and increased platelet count were observed in the 0.58 mg/kg group and increased inorganic phosphorus was observed in the 1.92 mg/kg group. None of these changes were observed at the higher dose and no changes were observed in related test parameters. These changes were considered not due to laninamivir octanoate. The NOAEL in this study was determined to be 5.76 mg/kg/day, the maximum possible dose.

3.(iii).A.(3) Genotoxicity studies (4.2.3.3-1 to 4.2.3.3-6)

Genotoxicity was evaluated by a bacterial reverse mutation assay (4.2.3.3-1), a chromosomal aberration assay using cultured mammalian cells (human lymphocytes) (4.2.3.3-3), mouse lymphoma TK assay (4.2.3.3-5), and an intraperitoneal mouse bone marrow micronucleus assay

(4.2.3.3-6). None of these studies showed genotoxicity of laninamivir octanoate. The active metabolite R-125489 was subjected to a bacterial reverse mutation assay (4.2.3.3-2) and a chromosomal aberration assay using cultured mammalian cells (Chinese hamster lung-derived fibroblasts) (4.2.3.3-4). No genotoxicity was detected.

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

Since the recommended clinical dosage regimen is single-dose administration, no carcinogenicity study was conducted. Laninamivir octanoate is not genotoxic, and the histopathological examination in the repeated inhalation studies did not detect any proliferative changes, cell necrosis, or increased regenerative changes in any tissues including the lungs. Based on these findings and the mechanism of action and the chemical structure of laninamivir octanoate, laninamivir octanoate is considered unlikely to have carcinogenicity.

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

Reproductive and developmental toxicity of laninamivir octanoate was investigated by the following studies by inhalation of the drug substance: a study of fertility and early embryonic development to implantation in rats, studies for effects on embryo-fetal development in rats and rabbits, and a study for effects on pre- and postnatal development, including maternal function, in rats. None of the studies showed effects on the reproductive function of parental animals, embryo-fetal development, or neonatal growth and development. Comparisons of the NOAEL in reproduction and development determined in each study with the exposure to the active metabolite R-125489 following the single dose inhalation of laninamivir octanoate 40 mg in Japanese healthy adult male subjects (phase I single dose study [Study CS8958-A-J102]) showed safety margins of C_{max} of ≥20 fold and of AUC[25] of ≥10 fold. In rats, placental transfer [see "3.(ii).A.(2) Distribution"] and excretion in milk [see "3.(ii).A.(4) Excretion"] of laninamivir octanoate were observed.

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (4.2.3.5-1)

Laninamivir octanoate (0 [air], 6.4, 19, 63 mg/kg/day [maximum possible dose]) was administered by inhalation to male rats from 4 weeks before mating up to the necropsy of female rats, and to female rats from 2 weeks before mating up to Gestation day 6. Reduced body weight gain was observed in males receiving laninamivir octanoate during the pre-mating administration period, but the changes were not correlated with dose and the extent was minor. The changes were considered to have no toxicological significance. Laninamivir octanoate had no effect on the reproductive capacity of parental animals or on the early development of embryos. In this study, the NOAEL was determined to be 63 mg/kg/day, the maximum possible dose, for general toxicity and reproductive capacity of parental animals and for the development of the offspring.

3.(iii).A.(5).2) Studies for effects on embryo-fetal development

(a) Study in rats (4.2.3.5-2)

Laninamivir octanoate (0 [air], 6.3, 19, 61 mg/kg/day [maximum possible dose]) was administered by inhalation to pregnant rats from Gestation day 6 to Gestation day 17. A high post-implantation loss rate was observed in the 61 mg/kg group, but it was within the range of the historical data, and was considered to have no toxicological significance. Laninamivir octanoate had no effect on the body weight, sex ratio, external appearance, visceral organs, or skeletons of fetuses. In this study, the NOAEL was determined to be 61 mg/kg/day, the maximum possible dose, for general toxicity and reproductive capacity of maternal animals and for the development of the offspring.

[25] The comparison was made using $AUC_{0\text{-}22h}$ in rats and $AUC_{0\text{-}24h}$ in humans and rabbits.

(b) Study in rabbits (4.2.3.5-3)

Laninamivir octanoate (0 [air], 8.6, 17, 31 mg/kg/day [maximum possible dose]) was administered by inhalation to pregnant rabbits from Gestation day 6 to Gestation day 18. No effect of laninamivir octanoate was observed. In this study, the NOAEL was determined to be 31 mg/kg/day, the maximum possible dose, for general toxicity and reproductive capacity of maternal animals and for the development of the offspring.

3.(iii).A.(5).3) Study for effects on pre- and postnatal development, including maternal function in rats (4.2.3.5-4)

Laninamivir octanoate (0 [air], 6.4, 19, 54 mg/kg/day [maximum possible dose]) was administered by inhalation to pregnant rats from Gestation day 6 to Postpartum day 20 (administration was interrupted from Gestation day 21 to the date of delivery to avoid the effect on delivery). In maternal animals, decreased food intake was observed during the gestation period in the 54 mg/kg group, whereas laninamivir octanoate had no effect on the reproductive function. In the neonates, decreased body weight was observed on 21 and 28 days after birth in the ≥6.4 mg/kg groups, but since the changes were minor and no effect on developmental/behavioral parameters was observed, they were considered to have no toxicological significance. In the ≥6.4 mg/kg groups, decreased food intake was observed in the offspring before and after mating, but the rate of body weight increase remained unchanged between before and after mating. Laninamivir octanoate had no effect on the reproductive capacity of the offspring. In this study, the NOAEL was determined to be 19 mg/kg/day for maternal animals and 54 mg/kg/day, the maximum possible dose, for the development and reproductive capacity of the offspring.

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

Ocular mucosal irritation study in rabbits (4.2.3.6-1)

The mixed powder of laninamivir octanoate and lactose hydrate prepared according to the clinical formulation (content of drug substance, 20%) or lactose hydrate alone was administered at the dose of 0.1 g for 2 days into the conjunctival sac of the left eye of female rabbits, and irritability was evaluated according to Draize method and Kay and Calandra method. Lacrimation was observed at 1 hour after administration both in the mixed powder group and in the lactose hydrate group, but both the mixed powder and lactose hydrate were considered to be practically non-irritating, based on the assessment criteria. Thus, the applicant determined that the formulation prepared according to the clinical one was not irritating to the ocular mucosa.

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

Antigenicity study in mice (4.2.3.7-1)

Laninamivir octanoate suspension with 0.5% carboxymethylcellulose-Na was administered subcutaneously at 0.01 or 0.1 mg/dose for 9 doses (once daily, thrice weekly for 3 consecutive weeks), or laninamivir octanoate prepared in Freund's complete adjuvant was administered subcutaneously at 0.01 or 0.1 mg/dose thrice biweekly, to female mice. Blood samples were collected at Week 1 after the last dose and tested for serum antibody titer by rat passive cutaneous anaphylactic (PCA) reaction. No PCA antibody titer was detected in the serum, and laninamivir octanoate was determined to be non-antigenic.

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

Effect on oral mucosa and systemic effect caused by swallowing

PMDA asked the applicant to discuss the effect of laninamivir octanoate on the oral mucosal membrane and the systemic effect caused by swallowing laninamivir octanoate.

The applicant responded as follows:

In the inhalation toxicity studies, laninamivir octanoate was administered to animals in a form of aerosol by spraying it into their nasal cavities because of their nose breathing habit. Therefore, the direct exposure of the oral mucosa to laninamivir octanoate was too low to evaluate the direct

effect. However, the toxicity studies in rats and dogs did not find treatment-caused abnormalities including histopathological changes in the respiratory mucosa (stratified squamous epithelium, pseudostratified ciliated epithelium) from the nasal cavities through the lungs including the larynx and trachea or in the tongue (stratified squamous epithelium). In the ocular mucosal irritation study in rabbits, laninamivir octanoate had no irritant effect on the mucous membrane. Based on these results, laninamivir octanoate is assumed to have no effect on the oral mucosa (stratified squamous epithelium). The results of the pharmacokinetic study showed that the oral absorption rates of laninamivir octanoate and the active metabolite R-125489 in rats treated with an oral dose of laninamivir octanoate were as low as 0.3% and 3.5%, respectively [see "3.(ii).A.(1) Absorption"]. These results suggest that laninamivir octanoate is very unlikely to show a toxic effect by absorption after swallowing.

PMDA accepted the above response of the applicant. Although toxicity was not studied by intraoral or oral administration, PMDA considers that there is no particular concern about the irritant effect on the oral mucosa or the systemic effect caused by swallowing, taking account of the results of studies on ocular mucosal irritation and on oral absorption.

4. Clinical data

In all of the following studies, the dose of Inavir (hereinafter also referred to as "laninamivir octanoate") is expressed on a laninamivir octanoate basis. Inhalers used for the administration of laninamivir octanoate were Inhaler A unless specified otherwise.

4.(i) Summary of biopharmaceutic studies and associated analytical methods, summary of clinical pharmacology studies

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

In this application, data of the following studies on the pharmacokinetics of laninamivir octanoate were submitted: 4 phase I studies in Japanese healthy adult male subjects and healthy elderly subjects, a PK study using the inhaler for commercial use (TwinCaps), a clinical pharmacology study in subjects with decreased renal function and another in pediatric patients (≤15 years of age) with influenza virus infection, and a phase III study in patients with influenza virus infection. Also, equivalence of the *in vitro* inhalation characteristics between the inhaler for clinical studies of laninamivir octanoate (Inhaler A) and the inhaler for commercial use (TwinCaps) was evaluated.

In each of the clinical studies, the concentrations of laninamivir octanoate and the active metabolite R-125489 in the plasma and urine were measured by LC/MS/MS (lower limit of quantitation, 1 ng/mL).

4.(i).A.(1) Evaluation of the equivalence of *in vitro* inhalation characteristics (3.2.P.2-1)

The equivalence of the *in vitro* inhalation characteristics of Inhaler A and TwinCaps was evaluated using an Andersen cascade impactor (ACI). The test was carried out according to the inhalation test stipulated in the US and European Pharmacopoeias.[26,27] The equivalence of the *in vitro* inhalation characteristics between the 2 inhalers was assessed based on the equivalence of the fine particle dose (FPD) and the similarity of the particle size distribution. [redacted]

[26] General Chapters: <601> Aerosols, nasal sprays, metered-dose inhalers, and dry powder inhalers. In: The United States pharmacopeia: the national formulary. USP 32, NF 27. Rockville, Md.: United States Pharmacopeial Convention; 2009

[27] European Pharmacopeia Section 2.9.18. Preparation for Inhalation: aerodynamic assessment of fine particles. In: European Pharmacopoeia. 6th ed. Strasbourg, France: Council of Europe; 2008:287-300

[redacted][28]

4.(i).A.(2) Studies in healthy adults

4.(i).A.(2).1) Phase I single dose study in Japanese healthy male adults (5.3.3.1-1, Study CS8958-A-J102 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Laninamivir octanoate (5, 10, 20, 40 mg) was administered by inhalation in a single dose to 31 Japanese healthy male adults (the number of subjects included in the pharmacokinetics analysis), and the pharmacokinetics of laninamivir octanoate and R-125489 was investigated. The results were as shown in the following table.

Pharmacokinetic parameters following a single dose inhalation of 5, 10, 20, and 40 mg of laninamivir octanoate

	Parameter	Dose group			
		5 mg (N = 7)	10 mg (N = 8)	20 mg (N = 8)	40 mg (N = 8)
Laninamivir octanoate	$AUC_{0\text{-}tz}$ (ng·h/mL)	29.225	102.365	185.648	505.152
	$AUC_{0\text{-}inf}$ (ng·h/mL)	64.436[a)]	108.007	191.323	511.781
	C_{max} (ng/mL)	10.027	27.088	49.145	140.589
	t_{max} (h)	1.00	0.50	0.50	0.50
	$t_{1/2}$ (h)	1.87	1.65	1.70	1.80
	$Xu_{0\text{-}144h}$ (%)	1.841	2.590	2.317	2.651
R-125489	$AUC_{0\text{-}tz}$ (ng·h/mL)	NA	53.858	197.945	622.972
	$AUC_{0\text{-}inf}$ (ng·h/mL)	–[b)]	56.570[c)]	474.770[c)]	728.344[a)]
	C_{max} (ng/mL)	NA	5.670	10.130	23.619
	t_{max} (h)	4.00[d)]	4.00	4.00	4.00
	$t_{1/2}$ (h)	5.59[a)]	11.29	41.44	63.99
	$Xu_{0\text{-}144h}$ (%)	9.165	10.799	10.155	12.126

Geometric mean (median for t_{max}), NA: Not calculated because data contained zero values.
$AUC_{0\text{-}tz}$: Area under plasma concentration-time curve from time 0 up to the last quantifiable time point, $AUC_{0\text{-}inf}$: Area under plasma concentration-time curve from time 0 up to infinity, C_{max}: Maximum plasma concentration, t_{max}: Time to maximum plasma concentration, $t_{1/2}$: Elimination half-life in the terminal phase, $Xu_{0\text{-}t}$: Cumulative urinary excretion rate up to t hours after administration
a) N = 5, b) N = 0, c) N = 1, d) N = 6

4.(i).A.(2).2) Phase I single high dose study in Japanese healthy male adults (5.3.3.1-2, Study CS8958-A-J106 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Laninamivir octanoate (80, 120 mg) was administered by inhalation in a single dose to 16 Japanese healthy male adults, and the pharmacokinetics of laninamivir octanoate and R-125489 was investigated. The results were as shown in the following Table.

[28] [redacted]

Pharmacokinetic parameters following a single dose inhalation of 80 and 120 mg of laninamivir octanoate

	Parameter	Dose group	
		80 mg (N = 8)	120 mg (N = 8)
Laninamivir octanoate	$AUC_{0\text{-}tz}$ (ng·h/mL)	1254.984	1548.513
	$AUC_{0\text{-}inf}$ (ng·h/mL)	1272.828	1556.664
	C_{max} (ng/mL)	334.995	411.659
	t_{max} (h)	0.50	0.50
	$t_{1/2}$ (h)	5.66	2.87
	CL_R (mL/min)	37.00	35.15
	$Xu_{0\text{-}144h}$ (%)	3.479	2.723
R-125489	$AUC_{0\text{-}tz}$ (ng·h/mL)	1512.827	2042.067
	$AUC_{0\text{-}inf}$ (ng·h/mL)	1996.443	2530.623
	C_{max} (ng/mL)	47.044	64.819
	t_{max} (h)	4.00	4.00
	$t_{1/2}$ (h)	79.53	71.14
	CL_R (mL/min)	91.67	89.58
	$Xu_{0\text{-}144h}$ (%)	14.190	12.476

Geometric mean (median for t_{max})
CL_R: Renal clearance

Data of this study were combined with data of the phase I single dose study in healthy male adults (Study CS8958-A-J102) and examined for dose proportionality over the dose range of 5 to 120 mg. The relation between a dose and $AUC_{0\text{-}tz}$, C_{max}, or $Ae_{0\text{-}144h}$ (cumulative urinary excretion up to 144 hours after administration) adjusted for the dose of laninamivir octanoate or R-125489 had a trend toward higher values in the 80 mg group. However, the values of the other dose groups in the dose range studied were similar in each parameter.

4.(i).A.(2).3) Phase I multiple dose study in Japanese healthy male adults (5.3.3.1-4, Study CS8958-A-J103 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Laninamivir octanoate (20, 40 mg) was administered by inhalation twice daily (BID) for 3 days (once on the last day) to 12 Japanese healthy male adults, and pharmacokinetics of laninamivir octanoate and R-125489 was investigated. The results were as shown in the following table. In both dose groups, $AUC_{0\text{-}10h}$ and C_{max} of laninamivir octanoate were similar between Day 1 and Day 3, whereas $AUC_{0\text{-}10h}$ and C_{max} of R-125489 increased with multiple doses.

Pharmacokinetic parameters following multiple-dose inhalation of laninamivir octanoate 20 or 40 mg BID

	Dose group	Parameter	Day 1	Day 3
Laninamivir octanoate	20 mg (N = 6)	$AUC_{0\text{-}10h}$ (ng·h/mL)	354.719	319.839
		C_{max} (ng/mL)	91.121	79.445
		t_{max} (h)	0.50	0.50
		$t_{1/2}$ (h)	–	1.95
		CL_R (mL/min)	32.60	37.24
		$Xu_{0\text{-}10h}$ (%)	3.473	3.573
	40 mg (N = 6)	$AUC_{0\text{-}10h}$ (ng·h/mL)	700.079	635.039
		C_{max} (ng/mL)	177.859	160.131
		t_{max} (h)	0.50	0.50
		$t_{1/2}$ (h)	–	3.50
		CL_R (mL/min)	36.66	38.12
		$Xu_{0\text{-}10h}$ (%)	3.850	3.630
R-125489	20 mg (N = 6)	$AUC_{0\text{-}10h}$ (ng·h/mL)	119.025	215.430
		C_{max} (ng/mL)	15.858	26.131
		t_{max} (h)	4.00	4.00
		$t_{1/2}$ (h)	–	55.49
		CL_R (mL/min)	91.42	104.57
		$Xu_{0\text{-}10h}$ (%)	4.453	9.223
	40 mg (N = 6)	$AUC_{0\text{-}10h}$ (ng·h/mL)	211.312	409.065
		C_{max} (ng/mL)	28.406	49.239
		t_{max} (h)	4.00	4.00
		$t_{1/2}$ (h)	–	61.54
		CL_R (mL/min)	101.11	109.63
		$Xu_{0\text{-}10h}$ (%)	4.373	9.176

Geometric mean (median for t_{max})

4.(i).A.(2).4) PK study in Japanese healthy adult male subjects using the inhaler for commercial use (5.3.3.1-3, Study CS8958-A-J107 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Laninamivir octanoate (20, 40 mg) was administered by inhalation in a single dose using the inhaler for commercial use (TwinCaps) to 16 Japanese healthy male adults, and pharmacokinetics of laninamivir octanoate and R-125489 was investigated. The results were as shown in the following table.

Pharmacokinetic parameters following a single dose inhalation of 20 or 40 mg of laninamivir octanoate using TwinCaps

	Parameter	Dose group	
		20 mg (N = 8)	40 mg (N = 8)
Laninamivir octanoate	$AUC_{0\text{-}tz}$ (ng·h/mL)	432.945	988.267
	$AUC_{0\text{-}inf}$ (ng·h/mL)	438.828	993.870
	C_{max} (ng/mL)	140.317	317.654
	t_{max} (h)	0.250	0.250
	$t_{1/2}$ (h)	1.78	2.67
	CL_R (mL/min)	33.93	35.44
	$Xu_{0\text{-}144h}$ (%)	4.538	5.305
R-125489	$AUC_{0\text{-}tz}$ (ng·h/mL)	551.078	1070.229
	$AUC_{0\text{-}inf}$ (ng·h/mL)	684.680	1364.591
	C_{max} (ng/mL)	18.799	37.024
	t_{max} (h)	4.000	4.000
	$t_{1/2}$ (h)	66.03	72.65
	CL_R (mL/min)	82.88	105.58
	$Xu_{0\text{-}144h}$ (%)	18.785	23.125

Geometric mean (median for t_{max})

Data of this study with TwinCaps were compared with those from the phase I single dose study

(Study CS8958-A-J102) and the phase I single high-dose study (Study CS8958-A-J106), both of which used Inhaler A. The patterns of over-time change in the plasma concentrations of laninamivir octanoate and R-125489 were similar between the group used TwinCaps and the group used Inhaler A, and the concentrations were higher in the groups used TwinCaps than the other.

4.(i).A.(3) Studies in patients

4.(i).A.(3).1) Phase III study comparing the devices in adult patients with influenza virus infection (5.3.5.2-1, Study CS8958-A-J304 [20 to 20])

Laninamivir octanoate (40 mg) was administered by inhalation in a single dose using the inhaler for commercial use (TwinCaps) or one for clinical studies (Inhaler A) to 32 adult patients with influenza virus infection, and the pharmacokinetics of laninamivir octanoate and R-125489 was investigated. The results were as shown in the following table. Plasma concentrations of laninamivir octanoate and R-125489 were lower in the TwinCaps group as compared with the Inhaler A group at each time point of measurement, while the patterns of over-time changes were similar between the 2 groups.

Over-time changes in plasma concentrations following a single dose inhalation of 40 mg of laninamivir octanoate using TwinCaps or Inhaler A in adult patients with influenza virus infection

	Dose group	Plasma concentration (ng/mL)		
		1 hr post-dose	4 hr post-dose	120 hr post-dose
Laninamivir octanoate	TwinCaps group (N = 14)	124.202 ± 52.133	55.071 ± 26.457	BLQ
	Inhaler A group (N = 18)	165.446 ± 52.538	74.248 ± 18.079	BLQ
R-125489	TwinCaps group (N = 14)	13.399 ± 5.893	23.549 ± 10.835	1.874 ± 1.035
	Inhaler A group (N = 18)	17.066 ± 7.214	30.286 ± 10.039	2.719 ± 1.080

Arithmetic mean ± SD, BLQ: Below the limit of quantitation (1 ng/mL)

The results of this study were compared with changes in plasma concentrations of laninamivir octanoate and R-125489 following a single dose inhalation of laninamivir octanoate in healthy adults (Studies CS8958-A-J102, CS8958-A-J106, and CS8958-A-J107) (adjusted for dose of 40 mg). Over-time changes in the mean plasma concentrations in adults with influenza virus infection largely overlapped that in healthy adult subjects, suggesting that the pharmacokinetics in these groups is similar.

4.(i).A.(3).2) Clinical pharmacology study in pediatric patients (≤15 years of age) with influenza virus infection (5.3.3.2-1, Study CS8958-A-J204 [20 to 20])

Laninamivir octanoate was administered by inhalation at 20 or 40 mg in a single dose or 20 mg QD for 2 days to 30 pediatric patients (≤15 years of age) with influenza virus infection, and the pharmacokinetics of laninamivir octanoate and R-125489 was investigated. The results were as shown in the following table. The plasma concentration of laninamivir octanoate 1 hour after inhalation of 20 mg QD was similar between Day 1 and Day 2, whereas the plasma concentration of R-125489 was higher on Day 2 than on Day 1.

Plasma concentration over time following a single dose inhalation of 20 or 40 mg of laninamivir octanoate, or following a 2-day inhalation of 20 mg of laninamivir octanoate, in pediatric patients (≤15 years of age) with influenza virus infection

	Dose group		Plasma concentration (ng/mL)			
			1 hr after administration	4 hr after administration	24 hr after administration	144 hr after administration
Laninamivir octanoate	20 mg single-dose group (N = 8)		91.096 ± 53.718	32.018 ± 17.609	0.509 ± 0.741	BLQ
	40 mg single-dose group (N = 11)		204.747 ± 90.122	74.655 ± 31.357	1.143 ± 0.644	BLQ
	20 mg 2-day dose group (N = 11)	Day 1	118.509 ± 93.173	43.080[a)]	–	–
		Day 2	133.999 ± 85.552	–	–	0.102 ± 0.338
R-125489	20 mg single-dose group (N = 8)		12.036 ± 8.098	17.631 ± 10.048	5.325 ± 2.737	0.529 ± 0.762
	40 mg single-dose group (N = 11)		21.680 ± 7.659	32.665 ± 9.960	9.641 ± 2.993	2.019 ± 1.100
	20 mg 2-day dose group (N = 11)	Day 1	11.467 ± 6.952	21.130[a)]	–	–
		Day 2	18.426 ± 9.434	–	–	2.413 ± 1.456

Arithmetic mean ± SD, BLQ: Below the limit of quantitation (1 ng/mL)
a) N = 1

The over-time changes in the plasma concentrations of laninamivir octanoate and R-125489 in this study were compared with those after single-dose inhalation of laninamivir octanoate in adults (Studies CS8958-A-J102, CS8958-A-J106, CS8958-A-J107, and CS8958-A-J304) (adjusted for dose of 40 mg). The mean plasma concentration in children tended to be high as compared with adults, but the difference between children and adults was not as great as the individual variability among the adults.

4.(i).A.(4) Studies on intrinsic factors

4.(i).A.(4).1) Phase I study in Japanese elderly subjects (5.3.3.3-1, Study CS8958-A-J104 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Laninamivir octanoate was administered by inhalation at 40 mg in a single dose or at 20 mg QD for 2 days (to elderly only) to 12 healthy elderly subjects and 6 healthy non-elderly subjects to investigate the pharmacokinetics of laninamivir octanoate and R-125489. The results were as shown in the following table. C_{max} and $AUC_{0\text{-}inf}$ of laninamivir octanoate and R-125489 were lower in the elderly than in the non-elderly, while t_{max} values were similar between the 2 groups. In the elderly, $t_{1/2}$ of laninamivir octanoate was higher while CL_R and $Xu_{0\text{-}48h}$ of laninamivir octanoate and R-125489 were lower, and this suggested decreases in CL_R and absorption in the elderly as compared with the non-elderly. In the phase I study in relatively elder subjects with decreased renal function (Study CS8958-A-J105), $Xu_{0\text{-}48h}$ values of laninamivir octanoate and R-125489 in subjects with normal renal function (subjects aged 53-79 years receiving 20 mg of laninamivir octanoate) (2.350% and 7.947%, respectively) were similar to that observed in healthy male adults (subjects aged 20-23 years receiving 20 mg of laninamivir octanoate) (2.276% and 6.677%, respectively) in the phase I single dose study (Study CS8958-A-J102). In a population pharmacokinetics (PPK) analysis, age was not selected as a significant covariate of the relative bioavailability (F1). These findings were considered to suggest that the apparent decrease in the absorption in the elderly group of this study was not age-dependent but was of interindividual variability.

Pharmacokinetic parameters following a single dose inhalation of 40 mg of laninamivir octanoate in elderly and non-elderly subjects

	Parameter	Treatment group	
		Elderly (N = 6)	Non-elderly (N = 6)
Laninamivir octanoate	$AUC_{0\text{-}inf}$ (ng·h/mL)	379.102	654.135
	C_{max} (ng/mL)	83.391	179.707
	t_{max} (h)	0.50	0.50
	$t_{1/2}$ (h)	2.47	1.88
	CL_R (mL/min)	23.06	35.72
	$Xu_{0\text{-}48h}$ (%)	1.345	3.549
R-125489	$AUC_{0\text{-}inf}$ (ng·h/mL)	652.028	815.109
	C_{max} (ng/mL)	15.486	29.490
	t_{max} (h)	4.00	4.00
	$t_{1/2}$ (h)	67.48	60.36
	CL_R (mL/min)	69.14	97.70
	$Xu_{0\text{-}48h}$ (%)	4.454	9.185

Geometric mean (median for t_{max})

Pharmacokinetic parameters following multiple dose inhalation of 20 mg QD of laninamivir octanoate in elderly subjects

	Parameter	Day 1	Day 2
Laninamivir octanoate	$AUC_{0\text{-}24h}$ (ng·h/mL)	227.640	228.329
	C_{max} (ng/mL)	45.989	42.508
	t_{max} (h)	0.50	1.00
	$t_{1/2}$ (h)	–	2.31
	CL_R (mL/min)	22.79	25.71
	$Xu_{0\text{-}24h}$ (%)	1.554	1.762
R-125489	$AUC_{0\text{-}24h}$ (ng·h/mL)	144.729	206.073
	C_{max} (ng/mL)	10.479	13.311
	t_{max} (h)	4.00	4.00
	$t_{1/2}$ (h)	–	49.43
	CL_R (mL/min)	62.79	72.52
	$Xu_{0\text{-}24h}$ (%)	3.717	6.119

Geometric mean (median for t_{max}), N = 6

4.(i).A.(4).2) Clinical pharmacology study in subjects with decreased renal function (5.3.3.3-2, Study CS8958-A-J105 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Laninamivir octanoate (20 mg) was administered by inhalation in a single dose to 20 subjects with decreased renal function or with normal renal function (7 subjects, normal; 4 subjects, mild renal impairment; 5 subjects, moderate renal impairment; 4 subjects, severe renal impairment),[29] and the pharmacokinetics of laninamivir octanoate and R-125489 was investigated. The results were as shown in the following table. The C_{max}, $AUC_{0\text{-}inf,}$ and t_{max} of laninamivir octanoate did not change with the decrease in the renal function. In contrast, C_{max} of R-125489 was approximately 1.6 times higher in the moderate renal impairment group, and approximately 1.9 times higher in the severe renal impairment group, as compared with the normal function group; $AUC_{0\text{-}inf}$ was approximately 2 times higher in the moderate renal impairment group, and approximately 5 times higher in the severe renal impairment group, than in the normal function group; and t_{max} increased in the moderate and severe renal impairment groups as compared with the normal function group.

[29] Normal function group, CL_{CR} >80; mild renal impairment group, 50≤ CL_{CR} ≤80; moderate renal impairment group, 30≤ CL_{CR} <50; severe renal impairment group, CL_{CR} <30 (calculated by 24 hour method)

Pharmacokinetic parameters following a single dose inhalation of 20 mg of laninamivir octanoate in subjects with decreased renal function and subjects with normal renal function

	Parameter	Treatment group			
		Normal function group (N = 7)	Mild renal impairment group (N = 4)	Moderate renal impairment group (N = 5)	Severe renal impairment group (N = 4)
Laninamivir octanoate	$AUC_{0\text{-}inf}$ (ng·h/mL)	338.291	305.701	419.785	400.059
	C_{max} (ng/mL)	74.260	57.401	65.693	57.931
	t_{max} (h)	0.50	1.00	0.60	1.50
	$t_{1/2}$ (h)	2.29	2.56	2.70	3.52
	CL_R (mL/min)	25.99[a)]	18.49	10.47	6.46
	$Xu_{0\text{-}48h}$ (%)	2.350[a)]	1.752	1.349	0.785
R-125489	$AUC_{0\text{-}inf}$ (ng·h/mL)	569.723	629.192	1158.180	2804.129
	C_{max} (ng/mL)	15.837	14.468	25.052	29.866
	t_{max} (h)	6.00	5.00	6.00	12.00
	$t_{1/2}$ (h)	56.12	54.05	53.16	56.96
	CL_R (mL/min)	65.05[a)]	47.36	26.06	12.68
	$Xu_{0\text{-}48h}$ (%)	7.947[a)]	6.401	6.746	5.844

Geometric mean (median for t_{max}); a) N=6

4.(i).A.(4).3) Population pharmacokinetic (PPK) analysis (5.3.3.5-1)

PPK analyses of laninamivir octanoate and R-124589 were conducted using the plasma concentration data and urinary concentration data obtained from phase I studies in healthy male adults (Studies CS8958-A-J102, CS8958-A-J103, CS8958-A-J106, and CS8958-A-J107), the phase I study in healthy elderly (elderly PK study, Study CS8958-A-J104), the phase I study in subjects with decreased renal function (PK study in subjects with decreased renal function, Study CS8958-A-J105), and the pediatric PK study (Study CS8958-A-J204).[30] The PPK analysis used data on the plasma concentrations and urinary concentrations of laninamivir octanoate and R-125489 obtained from 143 subjects (113 healthy subjects and 30 pediatric patients with influenza virus infection) at a total of 4749 sampling points (plasma concentrations of laninamivir octanoate at 1316 sampling points, urinary concentration of laninamivir octanoate at 722 sampling points, plasma concentration of R-125489 at 1884 sampling points, data on urinary concentration of R-125489 at 827 sampling points). The final model included CL_{CR} (creatinine clearance) as the factor affecting CL10 (total body clearance of laninamivir octanoate), CL12 (renal clearance of laninamivir octanoate), and CL45 (renal clearance of R-125489), and body weight as the factor affecting CL14 (metabolic clearance from laninamivir octanoate to R-125489), V1 (distribution volume of laninamivir octanoate in the central compartment), and V4 (distribution volume of R-125489 in the central compartment).

Effects of body weight and CL_{CR} on $AUC_{0\text{-}inf}$ and C_{max} of laninamivir octanoate and R-125489 were investigated using the final model. A decrease in CL_{CR} had the most marked effect on $AUC_{0\text{-}inf}$ of R-125489 both in adult and pediatric subjects. In contrast, changes in body weight did not significantly affect any of the pharmacokinetic parameters of laninamivir octanoate or R-125489.

4.(i).B. Outline of the review by PMDA

4.(i).B.(1) Comparison between Inhaler A and TwinCaps

In the study to compare the inhalers (Study CS8958-A-J304), plasma concentrations of laninamivir octanoate and R-125489 were lower in the TwinCaps group than in the Inhaler A group. In contrast, in the laninamivir octanoate 20 and 40 mg groups in the phase I single dose

[30] The PPK analysis (NONMEM VI 2.0) of laninamivir octanoate was performed by using the 2-compartment model with the first order elimination process, and that of R-125489 was performed by using the 1-compartment model with the first order elimination process that took into account the metabolism of laninamivir octanoate in the circulating blood and the transfer into the circulating blood of the drug substance being metabolized to R-125489 in the lungs after inhalation of laninamivir octanoate.

study (Study CS8958-A-J102) using Inhaler A and the PK study using the commercial-use inhaler TwinCaps (Study CS8958-A-J107), values of AUC, C_{max}, etc., in the TwinCaps group were approximately 2 times higher than those in the Inhaler A group. PMDA asked the applicant to discuss whether or not the pharmacokinetics of laninamivir octanoate is different between Inhaler A and TwinCaps by taking account of the differences in the study designs and patient characteristics.

The applicant responded as follows:
In the study to compare the inhalers (Study CS8958-A-J304), only the difference observed in patient characteristics between the Inhaler A group and the TwinCaps group was smoking habit. However, since the PPK analysis showed that smoking habit was not a factor affecting the plasma concentrations significantly and thus is unlikely to affect the comparison of the pharmacokinetics. Although plasma concentrations of laninamivir octanoate and R-125489 were lower in the TwinCaps group as compared with the Inhaler A group, each of which concentration distribution patterns are similar with similar over-time changes. In addition, the pharmacokinetics of laninamivir octanoate being inhaled may vary by individual depending on the length and internal diameter of the airway or by the way the inhaler is used, and the observed difference in the pharmacokinetics between the Inhaler A group and the TwinCaps group is considered to be of individual variability.

Since there was no difference in the patient characteristics between the phase I single dose study (Study CS8958-A-J102) and the PK study using the commercial-use inhaler (Study CS8958-A-J107), it is unclear why AUC and C_{max} were higher in the latter study. However, in light of the fact that there was an additional time point (0.25 hours after administration) of blood sampling in the PK study with the commercial-use inhaler (Study CS8958-A-J107) as compared with the phase I single dose study (Study CS8958-A-J102), the difference in the time points of blood sampling was likely to have affected the calculation of some the pharmacokinetic parameters.

PMDA considers as follows:
In a comparison between the phase I single dose study using Inhaler A (Study CS8958-A-J102) and the PK study using the commercial-use inhaler TwinCaps (Study CS8958-A-J107), the values of AUC, C_{max}, etc. in the TwinCaps group were approximately 2 times higher than those in the Inhaler A group. Although the cause of the difference is unclear, these studies were conducted at different time points and based on different study designs including the blood sampling time points. PMDA therefore understands the difficulty of accurate comparison of the pharmacokinetic parameters between the 2 types of inhalers. In the study to compare the inhalers (Study CS8958-A-J304), the concentration distributions of laninamivir octanoate and R-125489 were compared, and the TwinCaps group was shown to have an overall trend of lower distribution levels than the Inhaler A group. Therefore, whether or not the difference in the concentration distributions between the 2 types of inhalers can affect the efficacy of the drug product should be verified based on the comparison of the efficacy results [see "4.(ii).B.(3).2) Equivalence between the inhaler used in clinical studies and one for the commercial product"].

4.(i).B.(2) Dosage and administration in patients with decreased renal function

In the PK study in subjects with decreased renal function (Study CS8958-A-J105), increased C_{max} and $AUC_{0\text{-}inf}$ of R-125498 were considered attributable to decreased renal function. Therefore, PMDA asked the applicant to explain its view on need for dose adjustment of the drug for patients with decreased renal function based on the record of adverse events occurred in this patient population (by severity) that were summarized to identify any adverse events that are unique to this patient population or of dose-dependent.

The applicant responded as follows:

In all clinical studies of laninamivir octanoate in patients with influenza virus infection, "patients who have renal impairment" were not enrolled as per the exclusion criterion. Therefore, the safety of laninamivir octanoate has not been confirmed in patients with influenza virus infection who have renal impairment. However, a summary was made based on eGFRs (estimated glomerular filtration rates)[31] on the renal function statuses and safety information of the patients who participated in the clinical studies (phase II single dose study in Japan [Study CS8958-A-J201], phase II study in Taiwan [Study CS8958-A-A202], phase II multiple dose study in Japan [Study CS8958-A-J203], global phase III study [Study CS8958-A-J301], study to compare inhalers [Study CS8958-A-J304]) as shown in the following table. The incidence of adverse events was slightly higher in patients with low eGFR than in patients with normal renal function. However, not every dose group showed this trend clearly. Also, since the adverse events observed in 2 or more patients with low eGFR (diarrhoea, protein urine present) did not require intervention, it is considered that there were no significant safety problems with laninamivir octanoate in this population.

Adverse events in adults with influenza virus infection classified by eGFR

	eGFR								
	<60 mL/min/1.73 m^2			≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2			≥90 mL/min/1.73m^2		
	No. of subjects	No. of subjects with event	Incidence (%)	No. of subjects	No. of subjects with event	Incidence (%)	No. of subjects	No. of subjects with event	Incidence (%)
All laninamivir octanoate groups [a)]	55	21	38.2	726	179	24.7	511	125	24.5
Laninamivir octanoate 5 mg group	4	1	25.0	46	11	23.9	29	9	31.0
Laninamivir octanoate 10 mg group	7	2	28.6	84	26	31.0	48	15	31.3
Laninamivir g octanoate 20mg group	21	11	52.4	261	71	27.2	180	46	25.6
Laninamivir octanoate 20 mg twice group	1	1	100	54	12	22.2	38	6	15.8
Laninamivir octanoate 40 mg group	22	6	27.3	281	59	21.0	216	49	22.7
Oseltamivir phosphate group	19	5	26.3	268	74	27.6	226	60	26.5
Placebo group [b)]	6	2	33.3	41	11	26.8	13	1	7.7

a) Excludes 3 subjects in whom eGFR could not be calculated because of missing serum creatinine value.
b) Excludes 2 subjects in whom eGFR could not be calculated because of missing serum creatinine value.

[31] In clinical studies in patients with influenza virus infection other than the pediatric PK study, body weight of subjects was not measured, precluding the calculation of CL_{CR} estimate from Cockcroft-Gault equation. Therefore, eGFR was calculated from serum creatinine, age, and sex.

Treatment-related adverse events in adults with influenza virus infection classified by eGFR

	eGFR								
	<60 mL/min/1.73 m^2			≥60 mL/min/1.73m^2 and <90 mL/min/1.73 m^2			≥90 mL/min/1.73 m^2		
	No. of subjects	No. of subjects with event	Incidence (%)	No. of subjects	No. of subjects with event	Incidence (%)	No. of subjects	No. of subjects with event	Incidence (%)
All laninamivir octanoate groups [a)]	55	7	12.7	726	83	11.4	511	54	10.6
Laninamivir octanoate 5 mg group	4	0	0.0	46	7	15.2	29	6	20.7
Laninamivir octanoate 10 mg group	7	0	0.0	84	10	11.9	48	11	22.9
Laninamivir octanoate 20 mg group	21	4	19.0	261	32	12.3	180	15	8.3
Laninamivir octanoate 20 mg twice group	1	0	0.0	54	5	9.3	38	1	2.6
Laninamivir octanoate 40 mg group	22	3	13.6	281	29	10.3	216	21	9.7
Oseltamivir phosphate group	19	2	10.5	268	43	16.0	226	24	10.6
Placebo group [b)]	6	0	0.0	41	3	7.3	13	0	0.0

a) Excludes 3 subjects in whom eGFR could not be calculated because of missing serum creatinine values.
b) Excludes 2 subjects in whom eGFR could not be calculated because of missing serum creatinine values.

After 20 mg of laninamivir octanoate was administered by inhalation in a single dose, C_{max} and $AUC_{0\text{-}inf}$ of R-125489 increased approximately 1.9- and 5-fold, respectively, in patients with severely decreased renal function as compared with patients with normal renal function. Results of clinical studies in healthy subjects showed that C_{max} and $AUC_{0\text{-}inf}$ of R-125489 increased roughly in proportion to the dose of laninamivir octanoate at 5 to 120 mg. Therefore, although 40 mg of laninamivir octanoate has never been administered by inhalation in a single dose to patients with severely decreased renal function, C_{max} and $AUC_{0\text{-}inf}$ of R-125489 in these patients was also assumed to increase approximately 1.9- and 5-fold, respectively, as compared with patients with normal renal function. No significant safety problem was observed up to 120 mg (3 times the dose of 40 mg) in the phase I single high-dose study in healthy male adults (Study CS8958-A-J106) and up to the highest total dose of 200 mg (40 mg BID for a total of 5 doses, which is 5 times the dose of 40 mg) in the phase I multiple dose study in healthy male adults (Study CS8958-A-J103). Therefore, significant safety problems were unlikely to occur even when $AUC_{0\text{-}inf}$ of R-125489 increased 5-fold following the single-dose administration of laninamivir octanoate 40 mg.

Based on these findings, the applicant considered that dose adjustment of laninamivir octanoate is unnecessary for patients with decreased renal function including those with severely decreased renal function.

PMDA considers the dosage and administration of laninamivir octanoate in patients with decreased renal function as follows:
Taking account of the above explanation, PMDA accepts the applicant's the claim that the dose adjustment with laninamivir octanoate is unnecessary for patients with decreased renal function including those severely decreased renal function. However, in light of the facts that (a) only a limited number of renally impaired patients with eGFR of <60 mL/min/1.73 m^2 were investigated in clinical studies and (b) there is a lack of consistency between the laninamivir octanoate 20 mg group with a trend of markedly high incidences of adverse events in patients with decreased renal function than in those with normal renal function and other dose groups without such an apparent trend. The investigation of the safety of single-dose administration of laninamivir octanoate 40

mg in patients with decreased renal function (particularly in patients with severely decreased renal function) is considered insufficient. Therefore, precautions are necessary for the dosage and administration of laninamivir octanoate in patients with decreased renal function and post-marketing information on the use in such patients should be collected. The details of these measures should be discussed based on the efficacy and safety results from the clinical studies submitted. [see "4.(ii).B.(3).3) Dosage and administration in patients with renal impairment"]

4.(i).B.(3) Concentrations in plasma and at target sites in the lungs in pediatric patients

Because the mean plasma concentrations of laninamivir octanoate and R-125489 tended to be higher in pediatric patients as compared with those in adults, PMDA asked the applicant to discuss whether or not the efficacy or safety of laninamivir octanoate in pediatric patients was affected by the difference between children and adults in the concentrations of laninamivir octanoate in plasma and at target sites in the lungs.

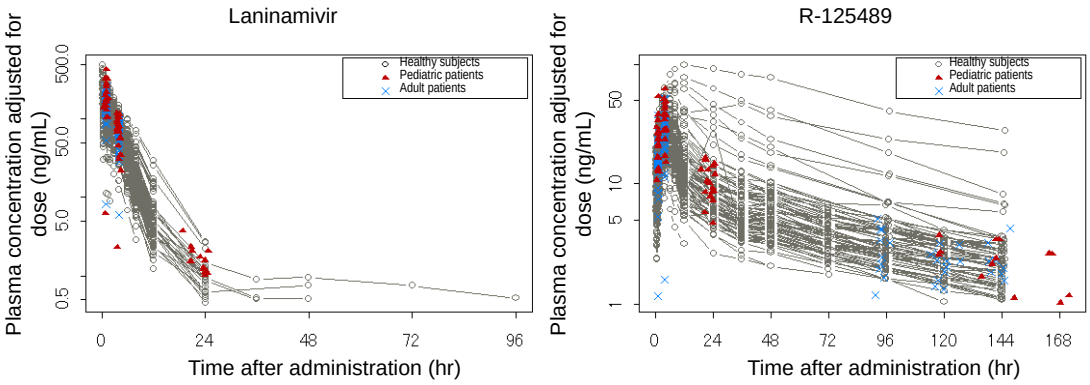
The applicant responded as follows:

The pharmacokinetics of laninamivir octanoate at target sites in the lungs in children and adults is unknown. However, TwinCaps (air resistance: [redacted] [cm H_2O]$^{1/2}$/[L/min]) has characteristics similar to those of HandiHaler (air resistance: 0.158 [cm H_2O]$^{1/2}$/[L/min]) used for tiotropium bromide hydrate, a commercially available inhaler. It is reported that HandiHaler enables ≥90% of patients with mild chronic obstructive pulmonary disease (COPD) and ≥70% of patients with moderate to severe COPD to inhale the drug at a flow speed of ≥20 L/min and in (*Respir Med*. 2007;101(11):2395-2401), which suggests that most COPD patients can inhale the drug at a flow speed of ≥20 L/min with TwinCaps as well.[32] The flow speed of 20 L/min is considered to roughly equivalent to that of patients who have lower inhaling capacity than male adults, such as children, women, and the elderly. Therefore, it is assumed that there is no difference in the volumes of FPD inhaled between children and adults.

The difference in plasma concentrations of laninamivir octanoate and R-125489 between children and adults was within the range of interindividual variability (see the figures below) in adults, and the PPK analysis showed that age was not a significant covariate. The PPK analysis also revealed no difference in estimated individual values of F1, a parameter that reflects the amount of laninamivir octanoate absorbed after being inhaled, between children and adults (except subjects aged ≥65 years).

It has also been confirmed that there was no clear relationship between the plasma concentrations of laninamivir octanoate or R-125489 and the clinical efficacy (time to alleviation of symptoms)of laninamivir octanoate, and that clinical studies revealed there was no significant difference in the overall incidence of adverse events between children and adults, [see "4.(ii).B.(2).1).(b) Children"]. Based on these findings, the applicant considers that the difference in plasma concentrations of laninamivir octanoate and R-125489 between children and adults will not affect the efficacy or safety of laninamivir octanoate in pediatric patients with influenza virus infection.

[32] An investigation on the relationship between the inhaling flow rate and FPD of laninamivir octanoate showed that FPD met the specifications when the inhaling flow rates (approximately [redacted]-[redacted] L/min) result in a pressure drop within the range from [redacted] to [redacted] kPa.



Plasma concentrations of laninamivir octanoate and R-125489 (adjusted for 40 mg of laninamivir octanoate)[33]

PMDA considers as follows:
PMDA understood that the difference between children and adults in the concentrations of laninamivir octanoate in target sites in the lungs was not investigated and therefore remains unclear. Also, PMDA accepted the applicant's response that although plasma concentrations of laninamivir octanoate and R-125489 were higher in children than in adults, the differences would not affect the efficacy or safety of laninamivir octanoate in pediatric patients with influenza virus infection, based on the following findings: (a) different plasma concentrations were confirmed to be due to interindividual variability, (b) there was no clear correlation between the plasma concentrations of laninamivir octanoate or R-125489 and the efficacy of laninamivir octanoate, and (c) no clear difference in the safety of laninamivir octanoate was observed between children and adults.

4.(i).B.(4) Absorption in the elderly

The applicant considers that the decreased absorption suggested in the elderly group in the elderly PK study (Study CS8958-A-J104) was not age-dependent but was due to interindividual variability. PMDA asked the applicant to discuss factors (including patient characteristics) affecting the interindividual variability in the pharmacokinetics (absorption) of laninamivir octanoate and R-125489 and to explain the concern for decreased clinical efficacy in the elderly.

The applicant responded as follows:
In the PPK analysis, the inter-individual variability of F1 was estimated to be 55% (coefficient of variation), while none of the investigated parameters (body weight, age, sex, pulmonary function, etc.) were found to have affected F1. These results suggested that the interindividual variability of F1 observed with laninamivir octanoate was attributable to other factors that were not investigated (e.g., interindividual difference in the length/internal diameter of the airway, handling of the inhaler, etc.). In the elderly PK study (Study CS8958-A-J104), the mean F1 in the elderly group was approximately 50.8% of that in the non-elderly group, but when the distribution of F1 in adults was compared with the data of clinical studies other than the elderly PK study, the mean F1 in the elderly (≥65 years of age) was close to the population mean and to the mean value of the non-elderly subjects (<65 years of age) (the mean F1 in the elderly was approximately 88.5%

[33] Results obtained after single-dose administration in each study (phase I single-dose study [Study CS8958-A-J102], phase I single high-dose study [Study CS8958-A-106], PK study using the inhaler for commercial use [Study CS8958-A-J107], elderly PK study [Study CS8958-A-J104], PK study in patients with decreased renal function [Study CS8958-A-J105], study to compare the inhalers [Study CS8958-A-J304], and pediatric PK study [Study CS8958-A-J204]) were plotted.

of that in the non-elderly subjects). Also, the data on the efficacy in elderly patients, even though limited, had no trend of any marked decrease in the efficacy as compared with non-elderly patients. Based on these results, the applicant considers that a decrease in the amount of laninamivir octanoate delivered to the lungs is unlikely to a risk of reduced efficacy of laninamivir octanoate in elderly patients.

PMDA considers as follows:
Because of the extremely small number of elderly patients investigated in clinical studies of laninamivir octanoate (8 patients in the 20 mg laninamivir octanoate group, 10 patients in the 40 mg laninamivir octanoate group [the combined number of patients aged ≥65 years in the global phase III study (Study CS8958-A-J301) and the study to compare the inhalers (Study CS8958-A-J304)]), a comparison of the efficacy of laninamivir octanoate is difficult between non-elderly patients and elderly patients. This precludes a clear determination that a decrease in the efficacy is unlikely to occur in the elderly. However, in the elderly PK study (Study CS8958-A-J104), F1 values varied significantly among individual patients, and a comparison of the distribution of F1 between the non-elderly and the elderly in clinical studies other than the elderly PK study showed similar mean F1 values between the 2 groups, failing to show clearly the effect of age on F1. In the PPK analysis, none of the parameters examined (including age) were identified as factors affecting F1. Taking account of these findings, PMDA understands the applicant's explanation that multiple factors other than age may affect the interindividual variability in the absorption of laninamivir octanoate.

4.(ii) Summary of clinical efficacy and safety

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

As the evaluation data, the results of the following studies were submitted in this application: 4 Japanese phase I studies in adults, 1 PK study using the inhaler for commercial use (TwinCaps), 2 clinical pharmacology studies in subjects with decreased renal function and in children (≤15 years of age), 2 Japanese phase II studies and 1 foreign phase II study, 1 Japanese phase III study and 1 global phase III study, 1 Japanese phase II/III study in pediatric subjects (≤9 years of age), and 1 Japanese phase III study in adolescents (10-19 years of age[34]). A summary of the submitted clinical studies are shown below.

[34] A study in patients 10 to 19 years of age at the time of informed consent

List of clinical studies

Region	Study number	Study subjects	N	Dosage and Administration[2)]	Treatment duration
Japan	CS8958-A-J102	Healthy male adults	40	Step 1: laninamivir octanoate 5 mg or placebo Step 2: laninamivir octanoate 10 mg or placebo Step 3: laninamivir octanoate 20 mg or placebo Step 4: laninamivir octanoate 40 mg or placebo	Single dose
Japan	CS8958-A-J106	Healthy male adults	20	Step 1: laninamivir octanoate 80 mg or placebo Step 2: laninamivir octanoate 120 mg or placebo	Single dose
Japan	CS8958-A-J107	Healthy male adults	16	Laninamivir octanoate 20 or 40 mg in TwinCaps	Single dose
Japan	CS8958-A-J103	Healthy male adults	16	Step 1: laninamivir octanoate 20 mg or placebo BID Step 2: laninamivir octanoate 40 mg or placebo BID	3 days (QD on Day 3)
Japan	CS8958-A-J104	Healthy elderly and healthy non-elderly	24	Elderly and non-elderly subjects: laninamivir octanoate 40 mg in a single dose Elderly subjects: laninamivir octanoate 20 mg QD for 2 days	Single dose or 2 days
Japan	CS8958-A-J105	Subjects with decreased renal function and subjects with normal renal function	20	Laninamivir octanoate 20 mg	Single dose
Japan	CS8958-A-J204	Pediatric patients (≤15 years of age) with influenza A or B virus infection	33	Laninamivir octanoate 20 or 40 mg in a single dose, or Laninamivir octanoate 20 mg QD for 2 days	Single dose or 2 days
Japan	CS8958-A-J201	Patients with influenza A or B virus infection	322	Laninamivir octanoate: 5 mg, 10 mg, or 20 mg Oseltamivir phosphate: 75 mg (as oseltamivir octanoate) BID (oral administration)	Laninamivir octanoate: single dose Oseltamivir phosphate: 5 days
Foreign countries	CS8958-A-A202	Patients with influenza A or B virus infection	180	Laninamivir octanoate 10 or 20 mg, or placebo	Single dose
Japan	CS8958-A-J203	Patients with influenza A or B virus infection	187	Laninamivir octanoate: 20 mg QD for 2 days Oseltamivir phosphate: 75 mg (as oseltamivir octanoate) BID (oral administration)	Laninamivir octanoate: 2 days Oseltamivir phosphate: 5 days
East Asia[1)]	CS8958-A-J301	Patients with influenza A or B virus infection	999	Laninamivir octanoate: 20 or 40 mg QD Oseltamivir phosphate: 75 mg (as oseltamivir octanoate) BID (oral administration)	Laninamivir octanoate: single dose Oseltamivir octanoate phosphate: 5 days
Japan	CS8958-A-J302	Pediatric patients (≤9 years of age) with influenza A or B virus infection	185	Laninamivir octanoate: 20 or 40 mg QD Oseltamivir phosphate: 2 mg/kg (as oseltamivir) BID (or 75 mg BID in patients weighing ≥37.5 kg) (oral administration)	Laninamivir octanoate: single dose Oseltamivir phosphate: 5 days
Japan	CS8958-A-J303	Adolescent patients (10-19 years old) with influenza A or B virus infection	120	Laninamivir octanoate: 20 or 40 mg	Single dose
Japan	CS8958-A-J304	Patients with influenza A or B virus infection	182	Laninamivir octanoate 40 mg in TwinCaps or Inhaler A	Single dose

QD: Once daily administration, BID: Twice daily administration. In phase I studies, the study drug was to be administered under fasting conditions.

1) Conducted as a global clinical study in Japan, Korea, Hong Kong, and Taiwan.

2) Administered by inhalation using Inhaler A unless specified otherwise.

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

4.(ii).A.(1).1 Phase I single dose study in Japanese healthy male adults (5.3.3.1-1, Study CS8958-A-J102 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind study was conducted at a single center in Japan to evaluate the safety and pharmacokinetics of laninamivir octanoate[35] in Japanese healthy adult male subjects (target sample size, 40 [10 subjects in each step (8 subjects in the laninamivir octanoate group, 2 subjects in the placebo group), in 4 steps in total]).

Subjects received a single dose inhalation of laninamivir octanoate 5 mg or placebo in step 1, laninamivir octanoate 10 mg or placebo in step 2, laninamivir octanoate 20 mg or placebo in step 3, and laninamivir octanoate 40 mg or placebo in step 4.

All of the 40 subjects enrolled in the study (10 subjects in each step) received the study drug and were included in the safety analysis set.

Three adverse events (nasopharyngitis, C-reactive protein increased, white blood cell count increased) were observed in 1 subject in the laninamivir octanoate group in step 2, but the causal relationships of all the events with laninamivir octanoate were ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).2 Phase I single high-dose study in Japanese healthy adult male subjects (5.3.3.1-2, Study CS8958-A-J106 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind study was conducted at a single center in Japan to evaluate the safety and pharmacokinetics of laninamivir octanoate in Japanese healthy male adults (target sample size, 20 [10 subjects in each step (8 subjects in the laninamivir group, octanoate 2 subjects in the placebo group), in 2 steps in total]).

Subjects received a single dose inhalation of laninamivir octanoate 80 mg or placebo in step 1 and laninamivir octanoate 120 mg or placebo in step 2.

All of the 20 subjects enrolled in the study (10 subjects in each step) received the study drug and were included in the safety analysis set. In the laninamivir octanoate 80 mg group, 2 adverse events (white blood cell increased, neutrophil percentage increased) were observed in 1 subject, but a causal relationship with laninamivir octanoate were ruled out for the both events.

4.(ii).A.(1).3 PK study in Japanese healthy adult male subjects using the inhaler for commercial use (5.3.3.1-3, Study CS8958-A-J107 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An uncontrolled, randomized, open-label, parallel-group study was conducted at a single center in Japan to evaluate the pharmacokinetics of laninamivir octanoate in Japanese healthy male adults (target sample size, 16 [8 subjects in each treatment group]) using the inhaler for commercial use (TwinCaps).

Laninamivir octanoate 20 mg or 40 mg was administered by inhalation in a single dose.

All of the 16 subjects enrolled in the study (8 subjects in each treatment group) received the study drug and were included in the safety analysis set. No adverse events were observed in this study.

[35] Laninamivir octanoate was administered by inhalation using Inhaler A unless specified otherwise in the text. The dose is always expressed on a laninamivir octanoate basis

4.(ii).A.(1).4) Phase I multiple dose study in Japanese healthy male adults (5.3.3.1-4, Study CS8958-A-J103 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind study was conducted at a single center in Japan to evaluate the safety and pharmacokinetics of laninamivir octanoate in Japanese healthy adult male subjects (target sample size, 16 [8 subjects in each step [6 subjects in the laninamivir octanoate group, 2 subjects in the placebo group] in 2 steps in total]).

Laninamivir octanoate 20 mg or placebo was administered twice daily (BID) by inhalation in step 1 and laninamivir octanoate 40 mg or placebo was administered BID by inhalation in step 2. Both treatments were given for 3 days (once on Day 3).

All of the 16 subjects enrolled into the study (8 subjects in each treatment group) received the study drug, and were included in the safety analysis set.

One adverse event (nasopharyngitis) was reported by 1 subject in the laninamivir octanoate group in step 1. Its causal relationship of the adverse event with laninamivir octanoate was ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).5) Phase I study in Japanese healthy elderly (5.3.3.3-1, Study CS8958-A-J104 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind study was conducted at a single center in Japan to evaluate the safety and pharmacokinetics of laninamivir octanoate in Japanese healthy elderly subjects (≥65 years) and healthy non-elderly men (≥20 and ≤45 years) (target sample size, 24 [8 subjects in each age/treatment group (6 subjects in the laninamivir octanoate group, 2 subjects in the placebo group)]).

Laninamivir octanoate 40 mg or placebo was administered by inhalation in a single dose to both elderly and non-elderly subjects. Laninamivir octanoate was also administered by inhalation at a dose of 20 mg QD for 2 days to some elderly subjects.

All of the 24 subjects enrolled in the study (8 subjects in each age/treatment group) received the study drug and were included in the safety analysis set.

One adverse event (C-reactive protein increased) was observed in 1 elderly subject receiving a single dose of 40 mg of laninamivir octanoate, but its causal relationship of the adverse event with laninamivir octanoate was ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).6) Clinical pharmacology study in subjects with decreased renal function (5.3.3.3-2, Study CS8958-A-J105 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An uncontrolled, open-label study was conducted at a single center in Japan to evaluate the safety and pharmacokinetics of laninamivir octanoate in Japanese subjects with decreased renal function[36] (target sample size, 24 [6 subjects each in the normal renal function group, mild renal impairment group, moderate renal impairment group, and severe renal impairment group]).

Laninamivir octanoate 20 mg was administered by inhalation in a single dose.

All of the 20 subjects enrolled in the study (7 subjects in the normal renal function group, 4

[36] Renal function was classified as follows according to an estimate of CL_{CR} (mL/min) calculated by Cockcroft-Gault method: normal function group (CL_{CR} >80), mild impairment group (50≤ CL_{CR} ≤80), moderate impairment group (30≤ CL_{CR} <50), and severe impairment group (CL_{CR} <30).

subjects in the mild renal impairment group, 5 subjects in the moderate renal impairment group, 4 subjects in the severe renal impairment group) received the study drug and were included in the safety analysis set.

Adverse events observed include 5 events in 4 subjects in the normal function group (diarrhoea in 2 subjects, back pain in 1 subject, both neck pain and urobilin urine present in 1 single subject), 2 events in 2 subjects in the mild renal impairment group (hunger and blood urea increased), 2 events in 2 subjects in the moderate renal impairment group (diarrhoea and blood potassium increased in 1 subject each), and 3 events in 2 subjects in the severe renal impairment group (diarrhea in 1 subject, both alanine aminotransferase [ALT] increased and aspartate aminotransferase [AST] increased in 1 single subject). Of these, the adverse events assessed to be causally related to the study drug[37] (adverse drug reactions) were 1 event in 1 subject in the moderate renal impairment group (diarrhoea) and 2 events in 1 subject in the severe renal impairment group (ALT and AST increased observed at a test 48 hours after dosing). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).7) Clinical pharmacology study in pediatric patients (≤15 years of age) with influenza virus infection (5.3.3.2-1, Study CS8958-A-J204 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An uncontrolled, non-randomized, open-label study was conducted in 12 centers in Japan to evaluate the pharmacokinetics, safety, and efficacy of laninamivir octanoate in Japanese pediatric patients (≤15 years of age) with influenza A or B virus infection (target sample size, 30 [10 patients each in the laninamivir octanoate 20 mg single-dose group, laninamivir octanoate 40 mg single-dose group, and laninamivir octanoate 20 mg multiple-dose group]).

Laninamivir octanoate was to be administered by inhalation at a dose of 20 or 40 mg in a single dose or at a dose of 20 mg QD for 2 days.

All of the 33 patients enrolled in the study (9 patients in the laninamivir octanoate 20 mg single-dose group, 13 patients in the laninamivir octanoate 40 mg single-dose group, and 11 patients in the laninamivir octanoate 20 mg multiple-dose group) received the study drug and were included in the full analysis set (FAS), and the FAS was used for both efficacy analysis and safety analysis.

Efficacy assessment included investigation of time to alleviation of influenza symptoms and the time for body temperature to return to normal.

The median time to alleviation of influenza symptoms (criterion for body temperature, ≤36.9°C) (95% confidence interval [CI]) was 86.6 hours (19.5-NC [not calculated]) in the laninamivir octanoate 20 mg single-dose group, 104.8 hours (60.1-NC) in the laninamivir octanoate 40 mg single-dose group, and 67.3 hours (23.1-94.0) in the laninamivir octanoate 20 mg multiple-dose group. The difference in the median time to alleviation of influenza symptoms in the laninamivir octanoate 40 mg single-dose group relative to the laninamivir octanoate 20 mg single-dose group was 18.2 hours and that in the laninamivir octanoate 20 mg multiple-dose group relative to the laninamivir octanoate 20 mg single-dose group −19.3 hours. The median time to alleviation of influenza symptoms (criterion for body temperature,[38] ≤37.4°C) (95% CI) was 79.2 hours (19.5-

[37] In clinical studies submitted for this application, the causal relationship between an adverse event and the study drug was classified into 2 categories, "related" and "not related." An adverse events was assessed as "related" to the study drug if it met any of the following criteria: (i) It was considered to be due to the pharmacological effect or the toxicity of the study drug, (ii) no possible causal factors (e.g., primary disease of the subject, concurrent illness, past illness, concomitant drugs, concomitant therapies, or environmental factors) could be identified other than the pharmacological effect or the toxicity of the study drug, and (iii) the temporal relationship between the administration of the study drug and the occurrence of adverse events (including the clinical course after withdrawal of the study drug and the recurrence of adverse events after resumption of administration) cannot be excluded.

[38] In this report, normal body temperature is ≤37.4°C unless specified otherwise.

138.4) in the laninamivir octanoate 20 mg single-dose group, 91.8 hours (33.7-NC) in the laninamivir octanoate 40 mg single-dose group, and 45.6 hours (23.1-67.3) in the laninamivir octanoate 20 mg multiple-dose group. The difference in the median time to alleviation of influenza symptoms in the laninamivir 40 mg single-dose group relative to the laninamivir octanoate 20 mg single-dose group was 12.6 hours and that in the laninamivir octanoate 20 mg multiple-dose group relative to the laninamivir octanoate 20 mg single-dose group was −33.6 hours.

The safety analysis revealed the following adverse events noted: 2 events in 2 patients in the laninamivir octanoate 20 mg single-dose group (gastroenteritis rotavirus and epistaxis in 1 patient each); 2 events in 2 patients in the laninamivir octanoate 40 mg single-dose group (diarrhoea and ear pain in 1 patient each); and 3 events in 3 patients in the laninamivir octanoate 20 mg multiple-dose group (diarrhoea, otitis media acute, and skin erosion under the nose in 1 patient each). The adverse drug reaction noted was diarrhoea in 1 patient in the laninamivir octanoate 40 mg single-dose group and in 1 patient in the laninamivir octanoate 20 mg multiple-dose group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(2) Phase II studies

4.(ii).A.(2).1) Phase II single dose study in adult patients with influenza virus infection in Japan (5.3.5.1-1, Study CS8958-A-J201 [[redacted] to [redacted]])

An active-controlled, randomized, double-blind, parallel group study was conducted in 61 centers in Japan to evaluate the efficacy and safety of laninamivir octanoate in patients with influenza A or B virus infection (target sample size, 280 [210 patients in the laninamivir octanoate group, 70 patients in the oseltamivir phosphate group]).

In patients in the laninamivir octanoate group, a single dose of 5, 10, or 20 mg of laninamivir octanoate was administered by inhalation or placebo to match oseltamivir phosphate was orally administered BID for 5 days. In patients in the oseltamivir phosphate group, oseltamivir phosphate 75 mg (as oseltamivir) was to be orally administered BID for 5 days and a single dose of placebo to match laninamivir octanoate was to be administered by inhalation.

Of 324 patients enrolled in the study, 322 patients were included in FAS and the safety analysis set, and the remaining 2 patients were excluded because they withdrew consent. Of the 322 patients, a total of 278 patients in the safety analysis set were included in the per protocol set (PPS) and the PPS was used for the efficacy analysis. The remaining 44 patients were excluded: 13 patients who tested positive for influenza virus by a test kit but negative both by virus type identification test and anti-viral antibody test, 9 patients who used a prohibited concomitant drug during the study period, 8 patients who used drugs that could affect efficacy or safety evaluation, and 7 patients who had concurrent/past illness that could affect efficacy or safety evaluation (including duplicate counting).

The primary efficacy endpoint of median time for body temperature to return to normal (≤36.9°C) was 60.4 hours in the laninamivir octanoate 5 mg group, 54.6 hours in the laninamivir octanoate 10 mg group, 54.3 hours in the laninamivir octanoate 20 mg group, and 42.3 hours in the oseltamivir phosphate group. The differences in the median time for body temperature to return to normal (95% CI) in each laninamivir octanoate group relative to the oseltamivir phosphate group were as follows: 18.1 hours (0.9-23.4) in the laninamivir octanoate 5 mg group, 12.3 hours (−3.0 to 18.5) in the laninamivir octanoate 10 mg group, and 12.0 hours (−8.3 to 15.0) in the laninamivir octanoate 20 mg group. The upper limit of the 95% confidence interval being less than 24 hours in all laninamivir groups.

The safety analysis revealed that the incidence of adverse events was 26.6% (21 of 79 patients) in the laninamivir octanoate 5 mg group, 33.7% (28 of 83 patients) in the laninamivir octanoate

10 mg group, 41.6% (32 of 77 patients) in the laninamivir octanoate 20 mg group, and 33.7% (28 of 83 patients) in the oseltamivir phosphate group. The incidence of adverse drug reactions was 16.5% (13 of 79 patients) in the laninamivir octanoate 5 mg group, 19.3% (16 of 83 patients) in the laninamivir octanoate 10 mg group, 18.2% (14 of 77 patients) in the laninamivir octanoate 20 mg group, and was 24.1% (20 of 83 patients) in the oseltamivir phosphate group. Adverse events and adverse drug reactions with an incidence of ≥2% in any group were as shown in the following table.

Adverse events and adverse drug reactions with an incidence of ≥2% in any group

System organ class	Preferred term	Adverse events				Adverse drug reactions			
		Laninamivir octanoate 5 mg group (N = 79)	Laninamivir octanoate 10 mg group (N = 83)	Laninamivir octanoate 20 mg group (N = 77)	Oseltamivir phosphate group (N = 83)	Laninamivir octanoate 5 mg group (N = 79)	Laninamivir octanoate 10 mg group (N = 83)	Laninamivir octanoate 20 mg group (N = 77)	Oseltamivir phosphate group (N = 83)
Gastrointestinal disorders	Diarrhoea	7 (8.9)	9 (10.8)	6 (7.8)	11 (13.3)	6 (7.6)	9 (10.8)	4 (5.2)	11 (13.3)
	Enterocolitis	0 (0.0)	2 (2.4)	1 (1.3)	2 (2.4)	0 (0.0)	1 (1.2)	1 (1.3)	2 (2.4)
	Nausea	4 (5.1)	2 (2.4)	1 (1.3)	3 (3.6)	4 (5.1)	2 (2.4)	1 (1.3)	2 (2.4)
	Stomach discomfort	0 (0.0)	1 (1.2)	0 (0.0)	3 (3.6)	0 (0.0)	1 (1.2)	0 (0.0)	2 (2.4)
	Vomiting	1 (1.3)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Infections and infestations	Gastroenteritis	1 (1.3)	0 (0.0)	3 (3.9)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
	Nasopharyngitis	1 (1.3)	1 (1.2)	1 (1.3)	2 (2.4)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
	Oral herpes	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	ALT increased	0 (0.0)	0 (0.0)	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.9)	0 (0.0)
	AST increased	1 (1.3)	0 (0.0)	3 (3.9)	0 (0.0)	1 (1.3)	0 (0.0)	3 (3.9)	0 (0.0)
	White blood cell count increased	3 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	Dizziness	1 (1.3)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Upper respiratory tract inflammation	2 (2.5)	1 (1.2)	2 (2.6)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Number of patients with event (%)

Adverse events leading to treatment discontinuation were reported by 1 patient (acute sinusitis) in the laninamivir octanoate 20 mg group and 1 patient (nasopharyngitis) in the oseltamivir phosphate group. A causal relationship to the study drug was ruled out for all events. There were no serious adverse events or deaths.

4.(ii).A.(2).2) Phase II study in adult patients with influenza virus infection (5.3.5.1-2, Study CS8958-A-A202 in Taiwan [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel group study was conducted in 27 centers in Taiwan to evaluate the efficacy and safety of laninamivir octanoate in patients with influenza A or B virus infection (target sample size, 180 [120 patients in the laninamivir octanoate group, 60 patients in the placebo group]).

A single dose inhalation of 10 or 20 mg of laninamivir octanoate or placebo was to be administered.

Of 182 patients enrolled in the study, 174 patients were included in FAS except 8 patients (6 patients with no body temperature data available, 2 patients who never received the study drug). Of the patients included in the FAS, 147 patients (47 patients in the laninamivir 10 mg group, 53 patients in the laninamivir octanoate 20 mg group, 47 patients in the placebo group) were included in the PPS, and the PPS was used for the efficacy analysis. The remaining 27 patients were excluded: 13 patients who tested positive for an influenza virus test kit but negative for influenza infection either by virus type identification test or by anti-viral antibody test, 6 patients who used contraindicated concomitant drugs during the study period, and 5 patients who did not complete the administration of laninamivir octanoate or placebo. A total of 180 patients (58 patients in the laninamivir octanoate 10 mg group, 60 patients in the laninamivir octanoate 20 mg group, 62 patients in the placebo group) who received the study drug were included in the safety analysis set.

The primary efficacy endpoint of median time for body temperature to return to normal (intra-aural temperature ≤37.2°C) was 39.7 hours in the laninamivir octanoate 10 mg group, 38.5 hours

in the laninamivir octanoate 20 mg group, and was 41.0 hours in the placebo group. The differences in the median time (95% CI) in each laninamivir octanoate group relative to the placebo group were as follows: −1.3 hours (−13.5 to 7.5) in the laninamivir octanoate 10 mg group and −2.5 hours (−12.2 to 9.8) in the laninamivir octanoate 20 mg group. There was no significant difference in the time for body temperature to return to normal between each laninamivir octanoate group and the placebo group (generalized Wilcoxon test).

A secondary endpoint of median time to alleviation of influenza symptoms was 62.0 hours in the laninamivir octanoate 10 mg group, 49.9 hours in the laninamivir octanoate 20 mg group, and 84.0 hours in the placebo group. The difference in the median time to alleviation of influenza illness (95% CI) in each laninamivir octanoate group relative to the placebo group were as follows: −22.0 hours (−44.7 to 5.6) in the laninamivir octanoate 10 mg group and −34.1 hours (−43.8 to 4.4) in the laninamivir octanoate 20 mg group. The results showed a shorter time to alleviation of influenza symptoms in each laninamivir octanoate group as compared with the placebo group, although no significant differences were found (generalized Wilcoxon test).

The safety analysis revealed that the incidence of adverse events was 25.9% (15 of 58 patients) in the laninamivir octanoate 10 mg group, 21.7% (13 of 60 patients) in the laninamivir octanoate 20 mg group, and 22.6% (14 of 62 patients) in the placebo group. The incidence of adverse drug reactions was 8.6% (5 of 58 patients) in the laninamivir octanoate 10 mg group, 1.7% (1 of 60 patients) in the laninamivir octanoate 20 mg group, and was 4.8% (3 of 62 patients) in the placebo group. Adverse events and adverse drug reactions with an incidence of ≥2% in any group were as shown in the following table.

Adverse events and adverse drug reactions with an incidence of ≥2% in any group

System Organ Class	Preferred term	Adverse events			Adverse drug reactions		
		Laninamivir octanoate 10 mg group (N = 58)	Laninamivir octanoate 20 mg group (N = 60)	Placebo group (N = 62)	Laninamivir octanoate 10 mg group (N = 58)	Laninamivir octanoate 20 mg group (N = 60)	Placebo group (N = 62)
Gastrointestinal disorders	Diarrhoea	2 (3.4)	0 (0.0)	3 (4.8)	1 (1.7)	0 (0.0)	1 (1.6)
Investigations	ALT increased	1 (1.7)	0 (0.0)	2 (3.2)	1 (1.7)	0 (0.0)	0 (0.0)
	AST increased	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Haematocrit decreased	0 (0.0)	2 (3.3)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Haemoglobin decreased	0 (0.0)	2 (3.3)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Monocyte percentage increased	1 (1.7)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Protein urine present	0 (0.0)	2 (3.3)	2 (3.2)	0 (0.0)	1 (1.7)	0 (0.0)

Number of patients with event (%)

Adverse events leading to treatment discontinuation were reported by 1 patient (urinary tract infection) in the laninamivir octanoate 10 mg group, 1 patient (tonsillitis) in the laninamivir octanoate 20 mg group, and 1 patient (pharyngitis) in the placebo group. A causal relationship to the study drug was ruled out for all events. There were no serious adverse events or deaths.

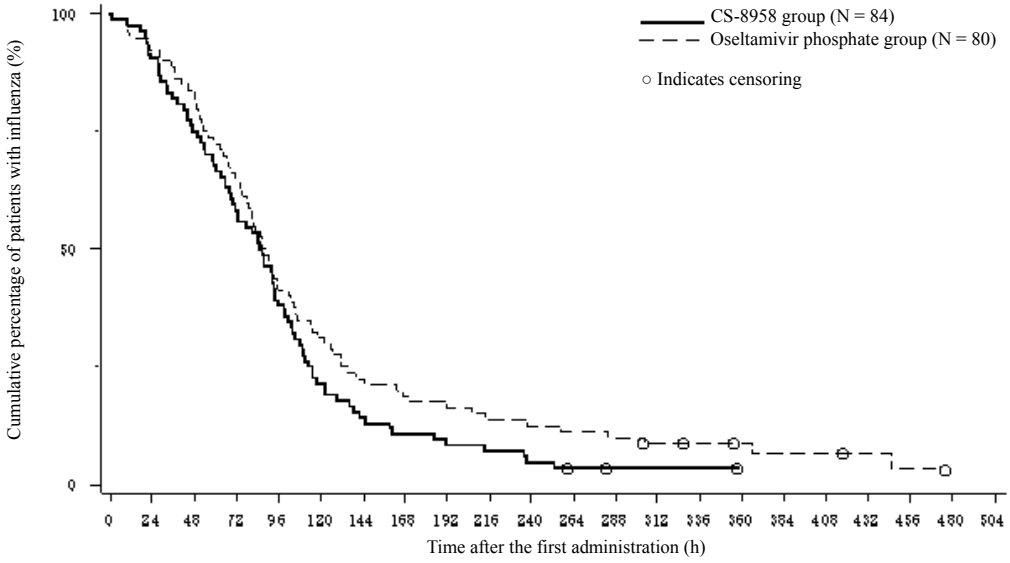
4.(ii).A.(2).3) Phase II multiple dose study in adult patients with influenza virus infection in Japan (5.3.5.1-4, Study CS8958-A-J203 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An active-controlled, randomized, double-blind, parallel group study was conducted in 21 centers in Japan to evaluate the efficacy and safety of laninamivir octanoate in patients with influenza A or B virus infection (target sample size, 140 [70 patients in the laninamivir octanoate group, 70 patients in the oseltamivir phosphate group]).

In patients in the laninamivir octanoate group, laninamivir octanoate 20 mg was administered QD for 2 days by inhalation or placebo to match oseltamivir phosphate was orally administered BID for 5 days. In patients in the oseltamivir phosphate group, oseltamivir phosphate 75 mg (as oseltamivir) was orally administered BID for 5 days or placebo to match laninamivir octanoate was administered QD for 2 days by inhalation.

All of the 187 patients enrolled in the study were included in FAS and in the safety analysis set. Of the 187 patients, 164 patients in the safety analysis set were included in the PPS, and the PPS was used for the efficacy analysis. The remaining 23 patients were excluded: 10 patients who were incompliant with the dosage and administration, 8 patients who tested positive for influenza virus by test kit but negative for influenza infection both by virus type identification test and anti-viral antibody test, 7 patients who used contraindicated concomitant drugs/therapies, and 1 patient who violated the inclusion/exclusion criteria (including duplicate counting).

The primary efficacy endpoint of median time to alleviation of influenza symptoms (95% CI) was 86.0 hours (69.2-93.5) in the laninamivir octanoate group and was 87.4 hours (77.1-103.1) in the oseltamivir phosphate group. The Kaplan-Meier curve of time to alleviation of influenza symptoms in each treatment group was as shown in the following figure. The difference in the median time to alleviation of influenza symptoms (95% CI) in the laninamivir octanoate group relative to the oseltamivir phosphate group was −1.4 (−27.6 to 7.3) hours.



Kaplan-Meier curves of duration of influenza illness (PPS)

The safety analysis revealed that the incidence of adverse events was 20.4% (19 of 93 patients) in the laninamivir octanoate group and 22.3% (21 of 94 patients) in the oseltamivir phosphate group. The incidence of adverse drug reactions was 6.5% (6 of 93 patients) in the laninamivir octanoate group and 7.4% (7 of 94 patients) in the oseltamivir phosphate group. Adverse events and adverse drug reactions with an incidence of ≥2% in either group were as shown in the following table.

Adverse events and adverse drug reactions with an incidence of ≥2% in either group

System Organ Class	Preferred term	Adverse events		Adverse drug reactions	
		Laninamivir octanoate group (N = 93)	Oseltamivir phosphate group (N = 94)	Laninamivir octanoate group (N = 93)	Oseltamivir phosphate group (N = 94)
Gastrointestinal disorders	Diarrhoea	1 (1.1)	3 (3.2)	1 (1.1)	3 (3.2)
	Nausea	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)
	Stomatitis	2 (2.2)	0 (0.0)	1 (1.1)	0 (0.0)
Infections and infestations	Gastroenteritis	1 (1.1)	2 (2.1)	0 (0.0)	0 (0.0)
	Nasopharyngitis	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)
Investigations	White blood cell count increased	1 (1.1)	2 (2.1)	0 (0.0)	2 (2.1)
Nervous system disorders	Headache	4 (4.3)	2 (2.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Cough	0 (0.0)	3 (3.2)	0 (0.0)	1 (1.1)

Number of patients with event (%)

Adverse events leading to treatment discontinuation were observed in 2 patients; bronchitis and tonsillitis in 1 patient each in the laninamivir octanoate group and bronchitis in 1 patient in the oseltamivir phosphate group. A causal relationship to the study drug was ruled out for all events. There were no serious adverse events or deaths.

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

4.(ii).A.(3).1) Global phase III study in adult patients with influenza virus infection (5.3.5.1-3, Study CS8958-A-J301 [[redacted] 20[redacted] to [redacted] 20[redacted]])

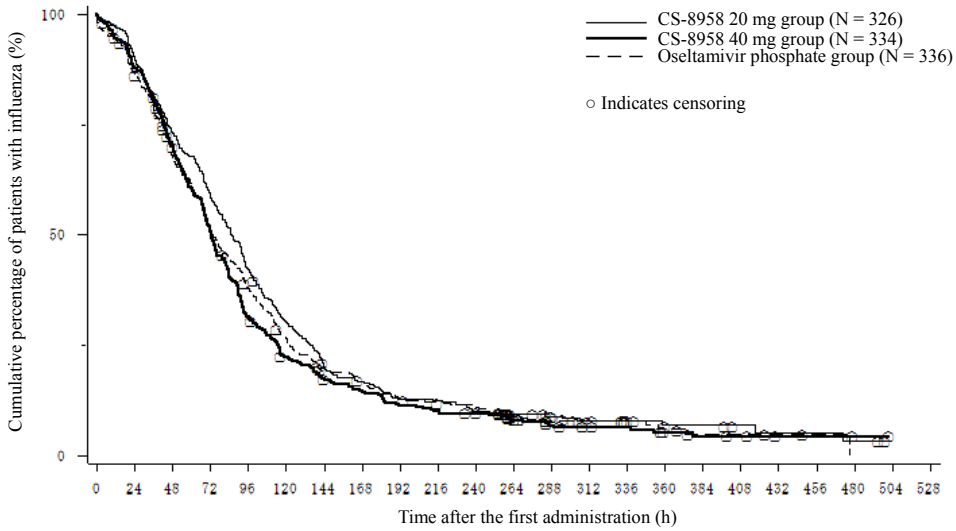
An active-controlled, randomized, double-blind, parallel group comparative study was conducted in 127 centers in Japan and other countries (103 centers in Japan, 14 centers in Taiwan, 7 centers in Hong Kong, 3 centers in Korea) to evaluate the efficacy and safety of laninamivir octanoate in patients with influenza A or B virus infection (target sample size, 900 [600 patients in the laninamivir octanoate group, 300 patients in the control group]).

In patients in the laninamivir octanoate group, a single dose of 20 or 40 mg of laninamivir octanoate was administered by inhalation or placebo to match oseltamivir phosphate was orally administered BID for 5 days. In patients in the control group, oseltamivir phosphate 75 mg (as oseltamivir) was orally administered BID for 5 days or a single dose of placebo to match laninamivir octanoate was administered by inhalation.

Of 1003 patients enrolled in the study (787 Japanese, 188 Taiwanese, 21 Koreans, 7 Hong Kongers), 999 patients (326 patients in the laninamivir octanoate 20 mg group, 337 patients in the laninamivir octanoate 40 mg group, 336 patients in the oseltamivir phosphate group) were included in the safety analysis set, and 4 patients were excluded (3 patients violating GCP, 1 patient untreated with the study drug). Of the 999 included in the safety analysis set, 996 patients were included in FAS and in the efficacy analysis set, and 3 patients were excluded (with no efficacy data).

The primary efficacy endpoint of median time to alleviation of influenza symptoms was 85.8 hours (76.5-92.8) in the laninamivir octanoate 20 mg group, 73.0 hours (68.4-80.8) in the laninamivir octanoate 40 mg group, and was 73.6 hours (68.5-83.3) in the oseltamivir phosphate group. The Kaplan-Meier curve of time to alleviation of influenza symptoms in each treatment group was as shown in the following figure. The differences (95% CI) of the median time to alleviation of influenza symptoms in each laninamivir octanoate group relative to oseltamivir phosphate group were as follows: 12.2 hours (−1.5 to 17.2) in the laninamivir octanoate 20 mg group and −0.6 hours (−9.9 to 6.9) in the laninamivir octanoate 40 mg group. In both laninamivir octanoate groups, the upper limit of the 95% confidence interval was below the pre-determined

non-inferiority margin (18 hours), verifying non-inferiority of the laninamivir octanoate 20 and 40 mg groups to oseltamivir phosphate group.



Kaplan-Meier curves of duration of influenza illness (FAS)

The safety analysis revealed that the incidence of adverse events was 25.5% (83 of 326 patients) in the laninamivir 20 mg group, 24.9% (84 of 337 patients) in the laninamivir octanoate 40 mg group, and was 26.8% (90 of 336 patients) in the oseltamivir phosphate group. The incidence of adverse drug reactions was 11.0% (36 of 326 patients) in the laninamivir octanoate 20 mg group, 13.1% (44 of 337 patients) in the laninamivir octanoate 40 mg group, and was 12.5% (42 of 336 patients) in the oseltamivir phosphate group. Adverse events and adverse drug reactions with an incidence of ≥2% in any group were as shown in the following table.

Adverse events and adverse drug reactions with an incidence of ≥2% in any group

System Organ Class	Preferred term	Adverse events			Adverse drug reactions		
		Laninamivir octanoate 20 mg group (N = 326)	Laninamivir octanoate 40 mg group (N = 337)	Oseltamivir phosphate group (N = 336)	Laninamivir octanoate 20 mg group (N = 326)	Laninamivir octanoate 40 mg group (N = 337)	Oseltamivir phosphate group (N = 336)
Gastrointestinal disorders	Diarrhoea	18 (5.5)	26 (7.7)	26 (7.7)	15 (4.6)	22 (6.5)	22 (6.5)
	Nausea	7 (2.1)	4 (1.2)	6 (1.8)	3 (0.9)	3 (0.9)	5 (1.5)
	Vomiting	1 (0.3)	1 (0.3)	8 (2.4)	1 (0.3)	1 (0.3)	5 (1.5)
Infections and infestations	Nasopharyngitis	3 (0.9)	12 (3.6)	8 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)

Number of patients with event (%)

Adverse events leading to treatment discontinuation were 5 events in 4 patients (pneumonia in 2 patients, both acute sinusitis and IVth nerve paralysis in 1 single patient, sinusitis in 1 patient) in the laninamivir octanoate 20 mg group, 4 events in 3 patients (both diarrhoea and bronchitis in 1 single patient, bronchopneumonia in 1 patient, abnormal dreams in 1 patient) in the laninamivir octanoate 40 mg group, and 1 event in 1 patient (Wallenberg syndrome) in the oseltamivir phosphate group. Except abnormal dreams, a causal relationship to the study drug was ruled out for all events.

Serious adverse events observed were enterocolitis bacterial[39] in 1 patient in the laninamivir octanoate 20 mg group and pneumonia and Wallenberg syndrome in 1 patient each in the oseltamivir phosphate group. A causal relationship to the study drug was ruled out for all events, and they were confirmed to have resolved or were improving. One patient in the laninamivir octanoate 40 mg group was found to be pregnant after taking the study drug and was to be followed up until delivery. No death occurred.

4.(ii).A.(3).2) Phase II/III study in pediatric patients (≤9 years of age) with influenza virus infection (5.3.5.1-5, Study CS8958-A-J302 [December 2008 to March 2009])

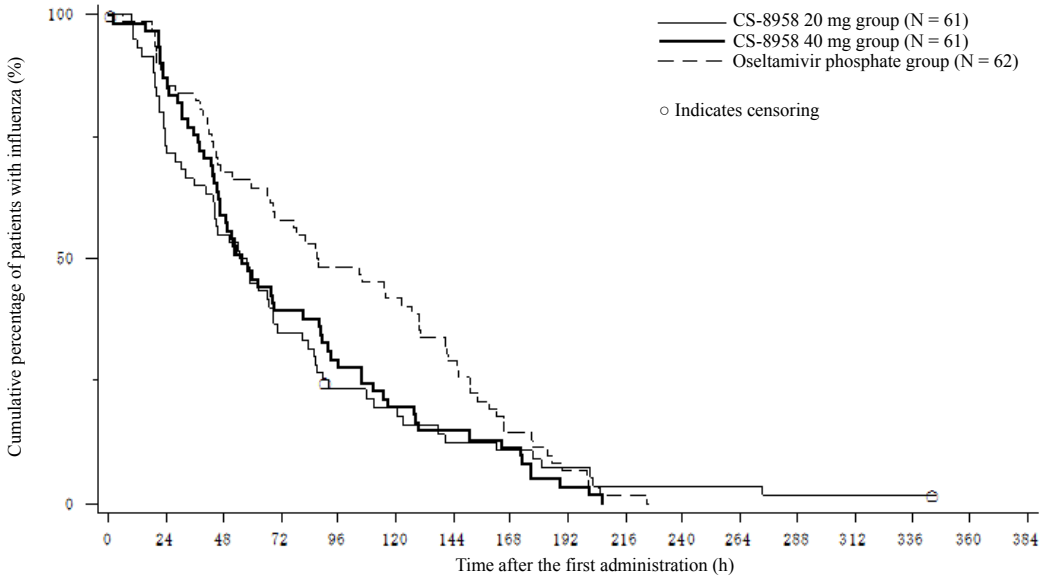
An active-controlled, randomized, double-blind, parallel group comparative study was conducted in 43 centers in Japan to evaluate the efficacy and safety of laninamivir octanoate in Japanese pediatric patients (≤9 years of age) with influenza A or B virus infection (target sample size, 180 [120 patients in the laninamivir octanoate group, 60 patients in the control group]).

In patients in the laninamivir octanoate group, a single dose of 20 or 40 mg of laninamivir octanoate was to be administered by inhalation or placebo to match oseltamivir phosphate was orally administered BID for 5 days. In patients in the oseltamivir phosphate group, oseltamivir phosphate 2 mg/kg (as oseltamivir), or oseltamivir phosphate 75 mg (as oseltamivir) in patients with body weight of ≥37.5 kg, was orally administered BID for 5 days and a single dose of placebo to match laninamivir octanoate was administered by inhalation.

Of 186 patients enrolled in the study, 185 patients (61 patients in the laninamivir octanoate 20 mg group, 62 patients in the laninamivir octanoate 40 mg group, 62 patients in the oseltamivir phosphate group) were included in the safety analysis set, except 1 patient (untreated with the study drug). Of the 185 patients included in the safety analysis set, 184 patients (61 patients in the laninamivir octanoate 20 mg group, 61 patients in the laninamivir octanoate 40 mg group, 62 patients in the oseltamivir phosphate group) were included in FAS as the efficacy analysis set, and 1 patient was excluded (no efficacy data).

The primary efficacy endpoint of median time to alleviation of influenza symptoms (95% CI) was 56.4 hours (43.7-69.2) in the laninamivir octanoate 20 mg group, 55.4 hours (46.3-81.3) in the laninamivir octanoate 40 mg group, and was 87.3 hours (67.9-129.7) in the oseltamivir phosphate group. The Kaplan-Meier curve of time to alleviation of influenza symptoms in each treatment group was as shown in the following figure. The difference (95% CI) in the median time to alleviation of influenza symptoms in each laninamivir octanoate group relative to the oseltamivir phosphate group was as follows: −31.0 (−50.3 to −5.5) hours in the laninamivir octanoate 20 mg group and −31.9 (−43.4 to 0.5) hours in the laninamivir 40 mg group. The results showed a significantly shorter time to alleviation of influenza symptoms in the laninamivir 20 mg group as compared with the oseltamivir phosphate group (generalized Wilcoxon test, $P = 0.0099$).

[39] Occurred 11 days after administration, which was out of the adverse event evaluation period



Kaplan-Meier curves of duration of influenza illness (FAS)

The safety analysis revealed that the incidence of adverse events was 34.4% (21 of 61 patients) in the laninamivir octanoate 20 mg group, 24.2% (15 of 62 patients) in the laninamivir octanoate 40 mg group, and was 38.7% (24 of 62 patients) in the oseltamivir phosphate group. The incidence of adverse drug reactions was 8.2% (5 of 61 patients) in the laninamivir octanoate 20 mg group, 4.8% (3 of 62 patients) in the laninamivir octanoate 40 mg group, and was 6.5% (4 of 62 patients) in the oseltamivir phosphate group. Adverse events and adverse drug reactions with an incidence of ≥2% in any group were as shown in the following table.

Adverse events and adverse drug reactions with an incidence of ≥2% in any group

System Organ Class	Preferred term	Adverse events			Adverse drug reactions		
		Laninamivir octanoate 20 mg group (N = 61)	Laninamivir octanoate 40 mg group (N = 62)	Oseltamivir phosphate group (N = 62)	Laninamivir octanoate 20 mg group (N = 61)	Laninamivir octanoate 40 mg group (N = 62)	Oseltamivir phosphate group (N = 62)
Gastrointestinal disorders	Diarrhoea	4 (6.6)	2 (3.2)	1 (1.6)	3 (4.9)	1 (1.6)	1 (1.6)
	Stomatitis	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Vomiting	3 (4.9)	2 (3.2)	4 (6.5)	2 (3.3)	1 (1.6)	2 (3.2)
Infections and infestations	Bronchitis	3 (4.9)	1 (1.6)	4 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Gastroenteritis	4 (6.6)	1 (1.6)	2 (3.2)	0 (0.0)	1 (1.6)	0 (0.0)
	Influenza	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Nasopharyngitis	1 (1.6)	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Sinusitis	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Epistaxis	1 (1.6)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Upper respiratory tract inflammation	3 (4.9)	4 (6.5)	4 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	Rash	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Number of patients with event (%)

Adverse events leading to treatment discontinuation were bronchitis in 1 patient in the laninamivir octanoate 20 mg group and influenza (reinfection) in 2 patients in the oseltamivir phosphate group. A causal relationship to the study drug was ruled out for all events. There were no serious adverse events or deaths.

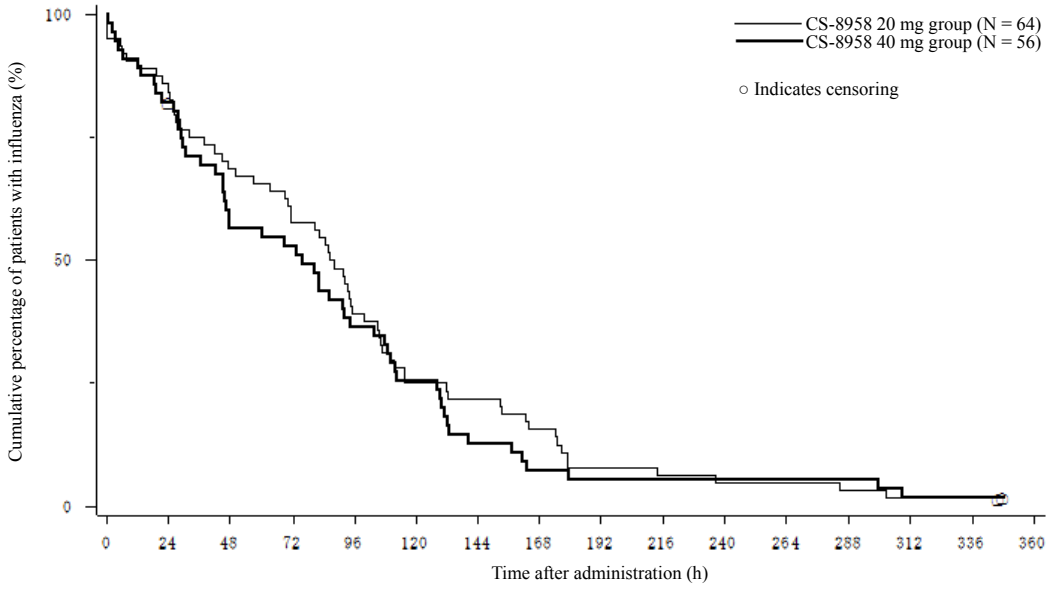
4.(ii).A.(3).3) Phase III study in adolescent patients (10-19 years of age) with influenza virus infection (5.3.5.1-6, Study CS8958-A-J303 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An uncontrolled, randomized, double-blind, parallel group comparative study was conducted in 33 centers in Japan to evaluate the safety and efficacy of laninamivir octanoate in Japanese adolescent patients (10-19 years of age) with influenza A or B virus infection (target sample size, 120 [60 patients in each treatment group]).

A single dose of 20 or 40 mg of laninamivir octanoate was administered by inhalation.

All of the 120 patients enrolled in the study (64 patients in the laninamivir octanoate 20 mg group, 56 patients in the laninamivir octanoate 40 mg group) were included in the FAS, and the FAS was used for the efficacy and safety analyses.

The primary efficacy endpoint of median time to alleviation of influenza symptoms (95% CI) was 87.1 hours (69.9-99.8) in the laninamivir octanoate 20 mg group and was 76.0 hours (45.4-94.3) in the laninamivir octanoate 40 mg group. The Kaplan-Meier curve of time to alleviation of influenza symptoms in each treatment group was as shown in the following figure. The difference (95% CI) in the median time to alleviation of influenza symptoms between the laninamivir octanoate 40 mg group and the laninamivir octanoate 20 mg group was −11.1 (−32.9 to 13.0) hours.



Kaplan-Meier curves of time to alleviation of influenza symptoms (FAS)

The safety analysis revealed the incidence of adverse events was 28.1% (18 of 64 patients) in the laninamivir octanoate 20 mg group and 28.6% (16 of 56 patients) in the laninamivir octanoate 40 mg group. The incidence of adverse drug reactions was 3.1% (2 of 64 patients) in the laninamivir octanoate 20 mg group and 5.4% (3 of 56 patients) in the laninamivir octanoate 40 mg group.

Adverse events and adverse drug reactions with an incidence of ≥2% in either group were as shown in the following table.

Adverse events and adverse drug reactions with an incidence of ≥2% in either group

System Organ Class	Preferred term	Adverse events		Adverse drug reactions	
		Laninamivir octanoate 20 mg group (N = 64)	Laninamivir octanoate 40 mg group (N = 56)	Laninamivir octanoate 20 mg group (N = 64)	Laninamivir octanoate 40 mg group (N = 56)
Gastrointestinal disorders	Diarrhoea	3 (4.7)	1 (1.8)	2 (3.1)	0 (0.0)
General disorders and administration site conditions	Pyrexia	3 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	Gastroenteritis	2 (3.1)	1 (1.8)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Epistaxis	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)
	Upper respiratory tract inflammation	2 (3.1)	3 (5.4)	0 (0.0)	0 (0.0)

Number of patients with event (%)

There were no adverse events leading to treatment discontinuation, neither were there deaths or serious adverse events.

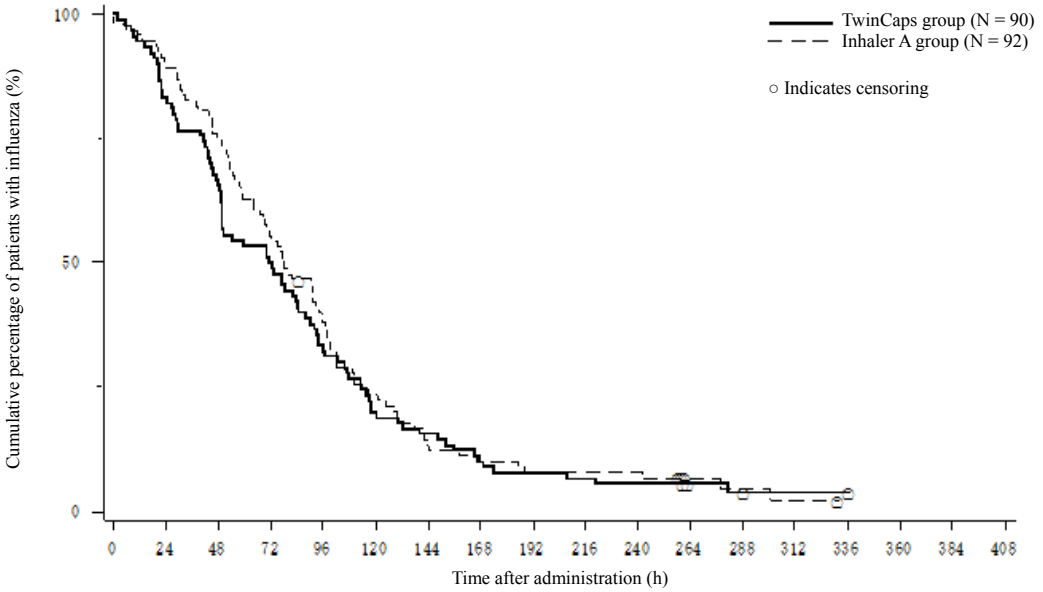
4.(ii).A.(3).4) Phase III study in adult patients with influenza virus infection to compare the inhalers (5.3.5.2-1, Study CS8958-A-J304 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, comparative study was conducted in 21 centers in Japan in patients with influenza A or B virus infection (target sample size, 140 [70 patients in each treatment group]) to compare the efficacy, safety, and pharmacokinetics following a single dose of laninamivir octanoate 40 mg administered with the inhaler for commercial use (TwinCaps) or the inhaler for clinical studies (Inhaler A).

A single dose of 40 mg of laninamivir octanoate was administered by inhalation using a TwinCaps or an Inhaler A.

Of 183 patients enrolled in the study, 182 patients (91 patients each in the TwinCaps group and in the Inhaler A group) were included in the FAS, and the FAS was used for the efficacy and safety analyses, while 1 patient untreated with laninamivir octanoate was excluded.

The primary efficacy endpoint of median time to alleviation of influenza symptoms (95% CI) was 72.0 hours (49.2-88.0) in the TwinCaps group and 78.0 hours (66.6-95.3) in the Inhaler A group. The Kaplan-Meier curve of time to alleviation of influenza symptoms in each treatment group was as shown in the following figure. The difference (95% CI) in the median time to alleviation of influenza symptoms between the TwinCaps group and the Inhaler A group was −6.0 (−23.9 to 6.7) hours.



Kaplan-Meier curves of time to alleviation of influenza symptoms (FAS)

The safety analysis revealed that the incidence of adverse events was 20.9% (19 of 91 patients) in the TwinCaps group and 12.1% (11 of 91 patients) in the Inhaler A group. The incidence of adverse drug reactions was 3.3% (3 of 91 patients) in the TwinCaps group and 6.6% (6 of 91 patients) in the Inhaler A group. Adverse events and adverse drug reactions with an incidence of ≥2% in either group were as shown in the following table.

Adverse events and adverse drug reactions with an incidence of ≥2% in either group

System Organ Class	Preferred term	Adverse event		Adverse drug reaction	
		TwinCaps group (N = 91)	Inhaler A group (N = 91)	TwinCaps group (N = 91)	Inhaler A group (N = 91)
Gastrointestinal disorders	Abdominal pain upper	3 (3.3)	0 (0.0)	1 (1.1)	0 (0.0)
	Diarrhoea	3 (3.3)	6 (6.6)	2 (2.2)	6 (6.6)
Infections and infestations	Bronchitis	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Nasopharyngitis	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)

Number of patients with event (%)

An adverse event leading to treatment discontinuation was bronchitis in 1 patient in the TwinCaps group, and a causal relationship of the event to the study drug was ruled out. There were no deaths or serious adverse events.

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

4.(ii).B.(1) Efficacy

PMDA evaluated the clinical efficacy of laninamivir octanoate in adults mainly based on the data from a Japanese phase II single dose study (Study CS8958-A-J201), a Taiwanese phase II study (Study CS8958-A-A202), a global phase III study (Study CS8958-A-J301), a Japanese phase II multiple dose study (Study CS8958-A-J203), and a phase III study to compare inhalers (the study to compare inhalers, Study CS8958-A-J304). The efficacy of laninamivir octanoate in pediatric patients was evaluated mainly based on the data from a phase II/III study in pediatric patients (≤9 years of age) (the study in patients aged ≤9 years, Study CS8958-A-J302) and a Japanese phase

III study in adolescent patients (10-19 years of age) (the study in patients aged 10 to 19 years, Study CS8958-A-J303).

4.(ii).B.(1).1) Method for efficacy evaluation

The primary endpoint of major clinical studies including confirmatory studies was the time to alleviation of influenza symptoms. In studies in adults, the time to alleviation of influenza symptoms was defined as a duration from the end of the first dose of the study drug to the time point at which all influenza symptoms (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, and cough) rated in the patient diary had become "none" or "mild" and remained at that level for ≥21.5 hours.

(a) Comparators in confirmatory studies

The applicant explained the appropriateness of oseltamivir phosphate as comparator for confirming the efficacy of laninamivir octanoate, as follows:

Currently in Japan, influenza virus infection is usually treated with an antiviral drug against influenza. In this situation, the use of a placebo as comparator for the evaluation of the efficacy of laninamivir octanoate would cause a reluctance of subjects to provide consent to their participation in the clinical studies, thereby reducing the feasibility of the clinical studies. Therefore, the use of an existing NA inhibitor, whose efficacy has been established to treat influenza virus infection, as comparator was decided. Zanamivir hydrate is also an inhaler, and its use as comparator would allow more accurate evaluation of adverse events unique to laninamivir octanoate. However, because of the difference in the dosage regimen between zanamivir hydrate and laninamivir octanoate, the use of the comparator would unnecessarily increase the frequency of inhalations of laninamivir octanoate in double-blind studies. In addition, the efficacy of zanamivir hydrate has not been confirmed in Japanese clinical studies,[40] and this may preclude the evaluation of the efficacy of laninamivir octanoate. Oseltamivir phosphate, however, having been found to be superior to placebo in the efficacy against influenza virus infection in Japanese and foreign clinical studies, is currently the most widely used drug for the treatment of influenza virus infection in Japan. For these reasons, the applicant considered that oseltamivir phosphate was the appropriate comparator. Since the use of oseltamivir phosphate in patients aged 10 to 19 years is generally discouraged,[41] the study of laninamivir octanoate in patients aged 10 to 19 years (Study CS8958-A-J303) was conducted without the comparator.

PDMA accepted the applicant's explanation on the selection of the comparator.

(b) Use of the data of foreign subjects

PMDA considers "time to alleviation of influenza symptoms" is appropriate as the primary efficacy endpoint, and yet asked the applicant to explain the strategy the applicant took to ensure the use of standardized criteria for alleviation of influenza symptoms among different ethnic groups, in the global phase III study (Study CS8958-A-J301) which was conducted in Japan, Taiwan, Korea, and Hong Kong.

The applicant responded as follows:

The definition of time to alleviation of influenza symptoms, which included specific influenza symptoms to be assessed and criteria for the alleviation of these symptoms, was the same as that used in clinical studies on oseltamivir phosphate in Japan and other countries.[42] The criteria for the alleviation of influenza symptoms depend on the severity of the symptoms assessed using the 4-grade scale (none, mild, moderate, severe). Therefore, in the global phase III study (Study CS8958-A-J301), concrete criteria for the severity of each symptom were made available to the

[40] The package insert of Relenza (October 2009)
[41] The package inserts of Tamiflu Capsule 75 and Tamiflu Dry Syrup 3% (September 2009)
[42] Tamiflu Capsule 75 [summary of product application] (December 2000)

subjects for the assessment of the severity of their own symptom.[43] Since the severity of influenza depends on subjective assessment by each subject, the concrete criteria for the severity of symptoms being described in objective terms were used in efforts to standardize assessment among subjects and especially among different ethnic groups.

PMDA asked the applicant to discuss possible ethnic differences in the efficacy outcome of the global phase III study (Study CS8958-A-J301).

The applicant responded as follows:
Results of the analysis of time to alleviation of influenza symptoms in each country/region participating in the global phase III study (Study CS8958-A-J301) (FAS) are shown in the following table. The numbers of subjects were extremely small in South Korea and Hong Kong as compared with the other 2 countries and this precluded the investigation of ethnic differences. Ethnic differences between Japan and Taiwan were discussed as follows.

Time to alleviation of influenza symptoms by country in global phase III study (Study CS8958-A-J301) (FAS)

	Japan			South Korea		
Parameter	Laninamivir octanoate 20 mg group N = 256	Laninamivir octanoate 40 mg group N = 263	Oseltamivir phosphate group N = 266	Laninamivir octanoate 20 mg group N = 7	Laninamivir octanoate 40 mg group N = 6	Oseltamivir phosphate group N = 5
Time to alleviation of influenza symptoms						
Median (hr) [a)]	79.5	71.6	72.1	91.8	44.3	108.2
95% CI [a)]	70.1-89.5	67.1-79.6	67.5-81.8	77.7-104.2	25.6-81.3	12.0-177.5
Difference from oseltamivir phosphate group (hr)	7.4	−0.5	–	−16.4	−63.9	–
95% CI of median difference	−6.1 to 13.0	−11.2 to 6.6	–	N.A.	N.A.	–
P value [b)]	0.4848	0.5995	–	0.8084	0.2416	–
	Taiwan			Hong Kong		
Parameter	Laninamivir octanoate 20 mg group N = 61	Laninamivir octanoate 40 mg group N = 62	Oseltamivir phosphate group N = 63	Laninamivir octanoate 20 mg group N = 2	Laninamivir octanoate 40 mg group N = 3	Oseltamivir phosphate group N = 2
Time to alleviation of influenza symptoms						
Median (hr) [a)]	119.3	88.6	86.9	N.C.	58.2	31.9
95% CI [a)]	94.8-139.1	69.8-113.7	55.0-113.8	N.A.	N.A.	N.A.
Difference from oseltamivir phosphate group (hr)	32.4	1.7	–	N.C.	26.3	–
95% CI of median difference	−2.6 to 62.1	−18.7 to 36.0	–	N.A.	N.A.	–
P value [b)]	0.0746	0.5626	–	N.A.	N.A.	–

[43] The 4-grade scale for the evaluation of symptoms were as follows: “none (no symptoms, the condition same as before illness),” “slightly disturbing (mild symptoms allowing normal daily activities),” “fairly disturbing (symptoms limiting daily activities to some extent),” and “intolerable (severe symptoms limiting daily activities, for example, difficulty in staying awake requiring medication”)

Parameter	Countries other than Japan (Taiwan + Korea + Hong Kong)			Total		
	Laninamivir octanoate 20 mg group N = 70	Laninamivir octanoate 40 mg group N = 71	Oseltamivir phosphate group N = 70	Laninamivir octanoate 20 mg group N = 326	Laninamivir octanoate 40 mg group N = 334	Oseltamivir phosphate group N = 336
Time to alleviation of influenza symptoms						
Median (hr) [a)]	113.8	79.1	84.8	85.8	73.0	73.6
95% CI [a)]	94.2-134.4	61.6-107.0	68.0-113.1	76.5-92.8	68.4-80.8	68.5-83.3
Difference from oseltamivir phosphate group (hr)	29.1	−5.7	–	12.2	−0.6	–
95% CI of median difference	0.3-58.8	−20.3 to 28.9	–	−1.5 to 17.2	−9.9 to 6.9	–
P value [b)]	0.0455	0.7333	–	0.1043	0.7481	–

N.A.: Not applicable because of the small number of subjects, N.C.: Not calculable
a) Estimated by the Kaplan-Meier method
b) Generalized Wilcoxon test using oseltamivir phosphate group as control

In both Japan and Taiwan, the median times to alleviation of influenza symptoms were similar between the laninamivir 40 mg group and the oseltamivir phosphate group, whereas that was longer in the laninamivir octanoate 20 mg group than in the other 2 groups. The following differences were observed between these countries/regions: (i) time to alleviation of influenza symptoms was longer in Taiwan than in Japan in all treatment groups, and (ii) this trend was marked particularly in the laninamivir octanoate 20 mg group in Taiwan.

In order to clarify the reason(s) for the longer time to alleviation of influenza symptoms in Taiwan, effects of background factors on time to alleviation of influenza symptoms were investigated by Cox regression analysis. Statistically significant differences were found in 3 factors, the total score of influenza symptoms at the start of treatment, sex, and presence/absence of influenza vaccination. With all these factors, time to alleviation of influenza symptoms tended to be longer in Taiwan as compared with those in Japan. This indicates that the differences in these background factors were the causes for the prolonged time to alleviation of influenza symptoms in Taiwan. In particular, the mean total score of influenza symptoms at the start of treatment, which was statistically highly significant as a covariate of Cox regression analysis, was 10.9 in Japan, while it was as high as 12.9 in Taiwan. These suggest that the primary reason why time to alleviation of influenza symptoms was longer in Taiwan than in Japan was that the total score of influenza symptoms at the start of treatment was higher in subjects in Taiwan than in Japan.

Discussion was also made on reasons for the markedly prolonged time to alleviation of influenza symptoms in Taiwan particularly in the laninamivir octanoate 20 mg group as compared with other 2 groups. More patients in the laninamivir octanoate 20 mg group in Taiwan had longer time to alleviation of symptoms despite the fact that their total score of influenza symptoms was not so high at the start of treatment. Therefore, patient characteristics were investigated in 13 patients in the laninamivir octanoate 20 mg group in Taiwan who had time to alleviation of influenza symptoms of ≥240 hours. The result revealed 12 of the 13 patients had A/H3N2 subtype. Time to alleviation of symptoms was then investigated by viral type (A/H1N1, A/H3N2 subtype) and by country (Japan, Taiwan), which showed that the median time to alleviation of influenza symptoms in the patient with A/H3N2 subtype in the laninamivir octanoate 20 mg group in Taiwan was 139.1 hours, longer than 107.7 hours in the patient with A/H1N1 subtype. In Taiwan, time to alleviation of influenza symptoms in patients with A/H3N2 subtype clearly showed great variability as compared with that in the patients with A/H1N1 subtype, which was prominent in some patients. This may have contributed to the higher median time to alleviation of influenza symptoms in the laninamivir octanoate 20 mg group in Taiwan.

Thus, the longer time to alleviation of symptoms in Taiwan than in Japan in all treatment groups is considered to be primarily due to the difference in the total score of influenza symptoms at the start of treatment. In addition, the interaction between country (Japan, Taiwan) and treatment group (laninamivir octanoate 20 mg, laninamivir octanoate 40 mg, oseltamivir phosphate) was not statistically significant (Cox regression analysis,[44] $P = 0.2269$). The applicant therefore considers that there was no ethnic difference in the efficacy outcome of the global phase III study (Study CS8958-A-J301).

PMDA considers as follows:
Time to alleviation of influenza symptoms was longer in Taiwan than in Japan in all treatment groups, and this trend was marked in the laninamivir octanoate 20 mg group in Taiwan. As explained by the applicant, characteristics of patients such as the total score of influenza symptoms at the start of treatment and the variability in time to alleviation of influenza symptoms may have contributed to the differences in efficacy between countries. Given that times to alleviation of symptoms were similar between the laninamivir octanoate 40 mg group and the oseltamivir phosphate group both in Japan and in Taiwan and that the analysis result by Cox-proportional hazard model adjusted for the effect of the difference in the total score of influenza symptoms at the start of treatment, etc., revealed no statistically significant interactive effects between country and treatment group including the laninamivir 20 mg group, PMDA considers that the efficacy of oseltamivir phosphate and that of laninamivir octanoate does not differ significantly between the 2 countries.

Based on these findings, PMDA accepted the explanation of the applicant and concluded that there were no particular problems in evaluating the efficacy of laninamivir octanoate based on the results of the global phase III study (Study CS8958-A-J301) including the data of foreign patients. However, time to alleviation of influenza symptoms was markedly longer in the laninamivir octanoate 20 mg group as compared with other groups. Therefore, taking this into account, a dose to be recommended should be carefully determined.

4.(ii).B.(1).2) Efficacy evaluation
Based on the following review on the efficacy of laninamivir octanoate in adults and children with influenza virus infection, PMDA concluded that the efficacy of laninamivir octanoate 40 mg in adults and children was confirmed.

(a) Efficacy of laninamivir octanoate (adults)
Times to alleviation of influenza symptoms in 5 studies subjected to efficacy evaluation were as shown below.

[44] Cox regression analysis performed using covariates including country (Japan, Taiwan), viral type, total score of influenza symptoms at the start of treatment, presence/absence of smoking habit, and presence/absence of influenza vaccination.

Summary statistics of time to alleviation of influenza symptoms in adults (FAS)

Study	Treatment group	N	Median[a] (hr) (95% CI)	Difference of median (hr) (95% CI)	*P* value[b]
Phase II single dose study (CS8958-A-J201)	Laninamivir octanoate 5 mg group	79	93.7 (72.4-107.9)	16.0 (−7.9 to 32.2)	0.2435
	Laninamivir octanoate 10 mg group	83	89.5 (71.5-99.8)	11.8 (−10.1 to 25.7)	0.4129
	Laninamivir octanoate 20 mg group	77	82.6 (70.7-103.5)	4.9 (−16.0 to 22.0)	0.7520
	Oseltamivir phosphate group	83	77.7 (64.7-97.8)	–	–
Phase II study in Taiwan (CS8958-A-A202)	Laninamivir octanoate 10 mg group	56	60.3 (39.2-72.2)	−29.2 (−50.1 to −1.6)	0.0323
	Laninamivir octanoate 20 mg group	59	51.3 (43.2-108.8)	−38.2 (−43.7 to 4.0)	0.1336
	Placebo group	58	89.5 (63.0-125.6)	–	–
Global phase III study (CS8958-A-J301)	Laninamivir octanoate 20 mg group	326	85.8 (76.5-92.8)	12.2 (−1.5 to 17.2)	0.1043
	Laninamivir octanoate 40 mg group	334	73.0 (68.4-80.8)	−0.6 (−9.9 to 6.9)	0.7481
	Oseltamivir phosphate group	336	73.6 (68.5-83.3)	–	–
Phase II multiple dose study (CS8958-A-J203)	Laninamivir octanoate 20 mg QD 2-day group	93	86.9 (70.7-98.6)	0.5 (−21.6 to 10.7)	0.5195
	Oseltamivir phosphate group	94	86.5 (75.0-95.6)	–	–
Study to compare inhalation containers (CS8958-A-J304)	Laninamivir octanoate 40 mg (TwinCaps) group	90	72.0 (49.2-88.0)	−6.0 (−23.9 to 6.7)	0.2550
	Laninamivir octanoate 40 mg (Inhaler A) group	92	78.0 (66.6-95.3)	–	–

The duration to assess alleviation of influenza symptoms, was 24 hours for the phase II single dose study (CS8958-A-J201) and phase II study in Taiwan (CS8958-A-A202), and 21.5 hours for the global phase III study (CS8958-A-J301), phase II multiple dose study (CS8958-A-J203), and the study to compare inhalers (CS8958-A-J304).
a) Estimated by the Kaplan-Meier method
b) Generalized Wilcoxon test

The applicant explained as follows:
In the phase II single dose study (Study CS8958-A-J201), the efficacy of a single dose inhalation of laninamivir octanoate 5, 10, and 20 mg was evaluated. The primary efficacy endpoint of time for body temperature to return to normal indicated that the single dose inhalation of laninamivir octanoate was effective against influenza infection. The median times for body temperature to return to normal were similar between the laninamivir octanoate 10 mg group and the 20 mg group, showing no statistically significant dose-response relationship. However, the higher dose was, the more effective the drug tended to be, and laninamivir octanoate 20 mg was thought to produce an effect most similar to oseltamivir phosphate. Nevertheless, even the maximum dose of 20 mg of laninamivir octanoate failed to show an adequate effect in time for body temperature to return to normal as compared with oseltamivir phosphate, suggesting that further dose increase would be more effective. To verify this possibility, the global phase III study (Study CS8958-A-J301) included a group to administer a single dose of laninamivir octanoate 40 mg by inhalation, in addition to the 20 mg single dose inhalation group. Also, in parallel with the global phase III study (Study CS8958-A-J301), a phase II multiple dose study was conducted with an additional group to be treated with laninamivir octanoate 20 mg QD 2-day inhalation to evaluate the efficacy of laninamivir octanoate in multiple doses. Based on the results of these 2 studies, the applicant was to determine clinical dosage and administration to be recommended. In the phase II study (Study CS8958-A-A202) in Taiwan, there was no significant difference in time for body temperature to return to normal between the laninamivir octanoate 10 mg group or 20 mg group and the placebo group, while time to alleviation of influenza symptoms tended to be shorter in both laninamivir octanoate groups than in the placebo group.

In the global phase III study (Study CS8958-A-J301), the primary endpoint of the median time to alleviation of symptoms in the FAS was 85.8 hours in the laninamivir octanoate 20 mg group, 73.0 hours in the laninamivir octanoate 40 mg group, and was 73.6 hours in the oseltamivir phosphate group. The difference (95% CI) in the median time to alleviation in each laninamivir octanoate group relative to the oseltamivir phosphate group was as follows: 12.2 (−1.5 to 17.2) hours in the laninamivir octanoate 20 mg group and −0.6 (−9.9 to 6.9) hours in the laninamivir octanoate 40 mg group. In both laninamivir octanoate groups, the upper limit of the 95% confidence interval was below the pre-determined non-inferiority margin (18 hours), verifying that laninamivir octanoate is effective against influenza A or B virus infection in adults.

Based on the non-inferiority of the laninamivir octanoate group to the oseltamivir phosphate group demonstrated in the global phase III study (Study CS8958-A-J301), PMDA considers that the efficacy of laninamivir octanoate in adult patients with influenza virus infection has been confirmed to be comparable to that of oseltamivir phosphate.

However, during the period when the global phase III study (Study CS8958-A-J301) was ongoing ([redacted] 20[redacted] to [redacted] 20[redacted]), most of A/H1N1 subtype strains were oseltamivir-resistant (Infectious Agents Surveillance Report [IASR] of Infectious Disease Surveillance Center, Information on the detection of seasonal influenza [A/H1N1] virus strains resistant to oseltamivir in the 2008/2009 season [http://idsc.nih.go.jp/iasr/rapid/pr3503.html]). In the global phase III study (Study CS8958-A-J301), which was conducted during the seasonal outbreak of A/H1N1 subtype virus with H275Y mutation (H275Y mutant virus[45]) that was considered resistant to oseltamivir phosphate, H275Y mutation was identified in 644 out of 646 samples collected from patients who had a diagnosis of infection with influenza virus of A/H1N1 subtype. In light of these findings, PMDA considered that the efficacy of laninamivir octanoate in this study should be examined more in detail while taking into account the possibility of compromised efficacy of the comparator oseltamivir phosphate. Therefore, PMDA asked the applicant to begin with an explanation on the clinical efficacy of oseltamivir phosphate against H275Y mutant virus, with reference to the Japanese and foreign guidelines and published literature on clinical research and studies.

The applicant responded as follows:
The guidelines on the treatment of influenza virus infection published by the World Health Organization (WHO) and by the Centers for Disease Control and Prevention (CDC) of the US[46,47] do not recommend monotherapy with oseltamivir phosphate against H275Y mutant virus. However, neither of these guidelines presents findings indicating reduced clinical efficacy of oseltamivir phosphate against H275Y mutant virus. Also, the urgent proposal of the Japanese Association for Infectious Diseases[48] states that oseltamivir phosphate "may still be effective in clinical use" against H275Y mutant virus.

Published literature on the clinical efficacy of oseltamivir phosphate against H275Y mutant virus suggests that oseltamivir phosphate still remains active against H275Y mutant virus based on a comparison with the febrile period in the no-treatment group.[49,50] A comparison between the 2007/08 season and the 2008/09 season shows a trend toward a decreased effect of oseltamivir phosphate against H275Y mutant virus. However, no difference was observed in changes in body

---

45 In "4. Clinical data" of this report, influenza A/H1N1 virus resistant to oseltamivir phosphate is expressed as "H275Y" based on N1-type NA instead of H274Y based on N2-type NA.

46 WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. (http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html)

47 Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. (http://www.cdc.gov/h1n1flu/recommendations.htm)

48 Urgent proposal of the Japanese Association for Infectious Diseases "How to respond to novel influenza in general practice," second edition (September 15, 2009) (http://www.kansensho.or.jp/topics/090914soiv_teigen2.html)

49 *Clin Infect Dis.* 2009;49(12):1828-35

50 *Clin Infect Dis.* 2006;43(4):439-44

temperature after the administration of oseltamivir phosphate or in virus reduction in patients aged ≥16 years, which suggests that the clinical efficacy of oseltamivir phosphate is maintained in adults even against H275Y mutant virus.[51]

In the phase II single dose study (Study CS8958-A-J201) conducted during the 2007/08 season, the influenza virus detected in 287 out of 309 patients who tested positive for (FAS) was of A/H1N1 subtype. The amino acid mutation H275Ywas identified in only 4 of these patients and most of A/H1N1 subtype strains isolated were oseltamivir-sensitive. In contrast, in the global phase III study (Study CS8958-A-J301) conducted during the 2008/09 season, most of A/H1N1 subtype strains isolated from subjects before the administration of the study drug had H275Y mutation. Therefore, the median times to alleviation of symptoms with A/H1N1 subtype in both studies (FAS) were compared between the laninamivir octanoate 20 mg group and the oseltamivir phosphate group, both of which were common to the 2 studies. In the phase II single dose study (Study CS8958-A-J201), times to alleviation of symptoms was 82.5 hours in the laninamivir octanoate 20 mg group and 77.7 hours in the oseltamivir phosphate group and, in the global phase III study (Study CS8958-A-J301), 82.9 hours in the laninamivir octanoate 20 mg group and 77.5 hours in the oseltamivir phosphate group, showing the almost similar results in the both studies. In the past clinical studies of oseltamivir phosphate, times to alleviation of symptoms in the placebo group was approximately 100 hours. These results suggest that the clinical efficacy of oseltamivir phosphate against H275Y mutant virus was maintained in the global phase III study (Study CS8958-A-J301) and support the findings of the published literature mentioned earlier.

For the global phase III study (Study CS8958-A-J301), the non-inferiority margin was determined to verify the non-inferiority of the laninamivir octanoate group to the oseltamivir phosphate group. As a value to ensure the efficacy of laninamivir octanoate, namely its superiority to placebo, the margin was selected based on the results of the past clinical studies of oseltamivir phosphate. Given that approximately 63% to 66% of patients in each treatment group were infected with H275Y mutant virus in the study (Study CS8958-A-J301), PMDA asked the applicant's view on whether or not the efficacy of laninamivir octanoate or its superiority to placebo can be ensured based on the non-inferiority of the laninamivir octanoate groups to the oseltamivir phosphate group as demonstrated in the global phase III study (Study CS8958-A-J301).

The applicant responded as follows:
The results of the past clinical studies of oseltamivir phosphate, which were referred to for defining the non-inferiority margin, and the result of the global phase III study (Study CS8958-A-J301) of laninamivir octanoate are shown in the following table.

[51] *J Infect.* 2009;59(3):207-12

Median times to alleviation of symptoms in past clinical studies of oseltamivir phosphate and in the global phase III study (Study CS8958-A-J301) of laninamivir octanoate

Study	Study code (country)	Placebo group	Oseltamivir phosphate group	Laninamivir octanoate 20 mg group	Laninamivir octanoate 40 mg group
Past clinical studies of oseltamivir phosphate[a)]	JV15823 study (Japan)	93.3 hr (N = 130)	70.0 hr (N = 122)	-	-
	WV15670 study (Europe, Canada, Hong Kong)	116.5 hr (N = 161)	87.4 hr (N = 158)	-	-
	WV15671 study (US)	103.3 hr (N = 129)	71.5 hr (N = 124)	-	-
	Combined analysis of WV15670, WV15671, and WV15730[b)] studies	112.5 hr (N = 309)	78.2 hr (N = 301)	-	-
Global phase III study (CS8958-A-J301) of laninamivir octanoate (Japan, Taiwan, Korea, Hong Kong)		-	73.6 hr (N = 336)	85.8 hr (N = 326)	73.0 hr (N = 334)

Data of the global phase III study (CS8958-A-J301) of laninamivir octanoate were obtained on the basis of the FAS.
a) Prepared from relevant data excerpted from the summary of data submitted in the initial application for oseltamivir phosphate (Summary of the application of "Tamiflu Capsule 75")
b) A study conducted in the southern hemisphere. Due to its small sample size (19 in the placebo group, 19 in the oseltamivir phosphate group), data of this study alone were omitted in the table.

In the past clinical studies of oseltamivir phosphate, the median times to alleviation of influenza symptoms in oseltamivir phosphate groups were 70.0 to 87.4 hours, whereas those in placebo groups were 93.3 to 116.5 hours, approximately 30 hours longer than the former, varying by time and region of the studies conducted. In the global phase III study (Study CS8958-A-J301) of laninamivir octanoate conducted during the 2008/09 season, time to alleviation of symptoms in the oseltamivir phosphate group was 73.6 hours, which was not significantly different from that in the past studies of oseltamivir phosphate.

Thus, according to these data and the results of the global phase III study (Study CS8958-A-J301) and the phase II single dose study (Study CS8958-A-J201), both of which involved infection with influenza virus of the A/H1N1 subtype, there was no outcome suggestive of reduced efficacy of oseltamivir phosphate against H275Y mutant virus in adult patients. Therefore, the applicant considers that the non-inferiority of laninamivir octanoate to oseltamivir phosphate demonstrated in the global phase III study (Study CS8958-A-J301) justifies the efficacy of laninamivir octanoate 20 and 40 mg or its superiority to placebo.

Based on the above discussion, PMDA considers the efficacy of the comparator oseltamivir phosphate and of laninamivir octanoate as follows:
The applicant's explanation (the non-inferiority of laninamivir octanoate to oseltamivir phosphate demonstrated in the global phase III study [Study CS8958-A-J301] justifies the efficacy of laninamivir octanoate 20 and 40 mg or its superiority to placebo), is convincing on the point that the efficacy of the active control oseltamivir phosphate as demonstrated in the global phase III study (Study CS8958-A-J301) has been maintained at the level of the previous seasons and this finding is supported by the following outcomes:

i) The comparison of the phase II single dose study (Study CS8958-A-J201) conducted during the 2007/08 season, during which few H275Y mutation was detected, and the global phase III study (Study CS8958-A-J301) conducted in the 2008/09 season showed that times to alleviation of symptoms in patients infected with influenza virus of A/H1N1 subtype in the oseltamivir phosphate groups in the two studies were similar.

ii) Time to alleviation of symptoms (73.6 hours) in the oseltamivir phosphate group of the global phase III study (Study CS8958-A-J301) was within the variation in the results of the past clinical studies (70.0-87.4 hours) that was used to justify the definition of the non-inferiority margin and was even close to the lower limit of the range.

On the other hand, taking account of the following reports of observational studies and the clinical studies of similar drugs, the possibility of reduced efficacy of oseltamivir phosphate due to the effect of H275Y mutant virus cannot be completely ruled out.

i) The major results of the published literature (*Clin Infect Dis.* 2009;49:1828-35, *J Infect.* 2009;59:207-212) cited by the applicant suggest reduced efficacy of oseltamivir phosphate against the A/H1N1 subtype in the 2008/09 season because of H275Y mutation, revealing that this trend was significant in children aged ≤15 years. However, these do not mean to suggest that the efficacy of oseltamivir phosphate was maintained in adults.

ii) In the clinical study data submitted in the application for a similar drug peramivir hydrate, the placebo group in the phase II study conducted in the 2007/08 season and the oseltamivir phosphate group in the study conducted in the 2008/09 season showed similar times to alleviation of symptoms (81.8 hours and 81.8 hours, respectively) (Review Report of "Rapiacta 300 mg bag for intravenous drip infusion, Rapiacta 150 mg vial for intravenous drip infusion," December 2009).

Time to alleviation of symptoms in the oseltamivir phosphate group may vary depending on the season of outbreak, patient characteristics and the distribution of virus types and subtypes that all differ from study to study. Further, time to alleviation of symptoms in the placebo group depends on the pathogenicity of H275Y mutant virus. When these findings are taken into consideration, it is difficult to reach a clear conclusion on the efficacy of oseltamivir phosphate as active control in the global phase III study (Study CS8958-A-J301) because no data were available on the placebo group in any clinical studies conducted in the 2008/09 season. At present, the Japanese and foreign guidelines have different opinions on the clinical efficacy of oseltamivir phosphate against H275Y mutant virus. However, since these opinions are not based on the results of clinical studies, further evidence should be collected by for example, conducting placebo-controlled comparative studies, so that the efficacy of oseltamivir phosphate against H275Y mutant virus can be clarified.

As described above, the applicant presented the interpretation that the non-inferiority of laninamivir octanoate to oseltamivir phosphate was demonstrated in the global phase III study (Study CS8958-A-J301). In response to this interpretation, PMDA discussed whether or not the superiority of laninamivir octanoate to placebo can be justified from viewpoints other than the efficacy of the active control, which is described below.

i) In the global phase III study (Study CS8958-A-J301), time to alleviation of symptoms was statistically significantly shorter in the laninamivir octanoate 40 mg group (73.0 hours) than in the concurrent control laninamivir octanoate 20 mg group, albeit the secondary analysis of the primary endpoint, (difference in median value [95% CI], −12.8 [−18.2 to −0.4] hours; generalized Wilcoxon test, $P = 0.0384$ without adjustment for multiplicity). The result suggests that the superiority of laninamivir octanoate to the putative placebo has been warranted at least at the dose of 40 mg.

ii) In the study in patients aged ≤9 years (Study CS8958-A-J302) conducted in the 2008/09 season, in which the global phase III study (Study CS8958-A-J301) was also conducted, time to alleviation of symptoms in the laninamivir octanoate 20 mg group was statistically significantly shorter than that in the oseltamivir phosphate group, although the comparison

was not made in a statistically powered confirmatory study used for the primary analysis. In addition, time to alleviation of symptoms was shorter in the laninamivir octanoate 40 mg group as well, albeit statistically insignificant, and this is considered to support the superiority of laninamivir octanoate 40 mg to placebo in adults.

Taking account of the discussions i) and ii), PMDA considered that the superiority of laninamivir octanoate has been warranted at lease at the dose of 40 mg. Thus, PMDA concluded that the demonstration of non-inferiority of laninamivir octanoate to oseltamivir phosphate in the global phase III study (Study CS8958-A-J301) had proved the efficacy of laninamivir octanoate 40 mg in adults with influenza virus infection.

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

(b) Efficacy of laninamivir octanoate (children)

The applicant explained the results of clinical studies in pediatric patients as follows:

The package insert of oseltamivir phosphate in Japan warns that the drug should not be used in adolescent patients aged ≥10 years as a rule,[52] precluding the use of the drug as comparator in clinical studies involving this age group. Therefore, the efficacy and safety of laninamivir octanoate in patients aged 10 to 19 years were evaluated in an uncontrolled, randomized, double-blind, dose-comparative study (in patients aged 10 to 19 years [Study CS8958-A-J303]).

In the study (Study CS8958-A-J302) conducted to evaluate the effect of laninamivir octanoate in pediatric patients (≤9 years of age) with influenza A or B virus infection, the primary endpoint of the median time to alleviation of symptoms[53] in the FAS was 56.4 hours in the laninamivir octanoate 20 mg group, 55.4 hours in the laninamivir octanoate 40 mg group, and was 87.3 hours in the oseltamivir phosphate group (see the table below). The difference (95% CI) in the median time to alleviation of symptoms as compared to the oseltamivir phosphate group was –31.0 (–50.3 to –5.5) hours in the laninamivir octanoate 20 mg group and was –31.9 (–43.4 to 0.5) hours in the laninamivir octanoate 40 mg group, showing a significantly shorter time in the laninamivir octanoate 20 mg group ($P = 0.0099$) than in the oseltamivir phosphate group, and the trend toward shorter time to alleviation of symptoms was also noted in the laninamivir octanoate 40 mg group ($P = 0.0591$).

In the study (Study CS8958-A-J303) conducted in adolescent patients (10-19 years of age) with influenza A or B virus infection, the primary endpoint of the median time to alleviation of symptoms[54] in FAS was 87.1 hours in the laninamivir octanoate 20 mg group and was 76.0 hours in the laninamivir octanoate 40 mg group. The difference (95% CI) in the median time between the laninamivir octanoate 40 mg group and the 20 mg group was –11.0 (–32.9 to 13.0) hours, showing a trend of shorter time to alleviation of symptoms in the laninamivir octanoate 40 mg group than in the laninamivir octanoate 20 mg group.

Based on these findings, the applicant considered that a single dose inhalation of laninamivir octanoate was effective in patients with influenza virus infection at both 20 mg and 40 mg.

---

[52] The package inserts of Tamiflu Capsule 75 and Tamiflu Dry Syrup 3% (September 2009)

[53] Time until cough and nasal symptoms improved to "none" or "mild" conditions with a decrease in body temperature to ≤37.4°C and these states persisted for ≥21.5 hours.

[54] Time point at which all influenza symptoms improved to "none" or "mild" in severity and remained at that state for ≥21.5 hours.

Summary statistics of times to alleviation of symptoms in children (≤9 years of age) and in adolescents (10-19 years of age) (FAS)

Study name	Treatment group	N	Median [a] (hr) (95% CI)	Comparison with oseltamivir phosphate group		Comparison between laninamivir octanoate groups	
				Difference of median (95% CI)	*P* value [b]	Difference of median (95% CI)	*P* value [b]
Study in patients aged ≤9 years (Study CS8958-A-J302) (criterion for body temperature, ≤37.4°C [primary endpoint])	Laninamivir octanoate 20 mg group	61	56.4 (43.7-69.2)	−31.0 (−50.3 to −5.5)	0.0099	-	-
	Laninamivir octanoate 40 mg group	61	55.4 (46.3-81.3)	−31.9 (−43.4 to 0.5)	0.0591	−1.0 (−9.0 to 22.4)	0.3720
	Oseltamivir phosphate group	62	87.3 (67.9-129.7)	-	-	-	-
Study in patients aged ≤9 years (Study CS8958-A-J302) (criterion for body temperature, ≤36.9°C [secondary endpoint])	Laninamivir octanoate 20 mg group	61	69.1 (60.5-96.5)	−41.2 (−48.5 to −4.7)	0.0178	-	-
	Laninamivir octanoate 40 mg group	61	81.3 (56.0-94.0)	−29.0 (−45.4 to −1.5)	0.0329	-	-
	Oseltamivir phosphate group	62	110.3 (86.8-140.3)	-	-	-	-
Study in patients aged 10 to 19 years (Study CS8958-A-J303)	Laninamivir octanoate 20 mg group	64	87.1 (69.9-99.8)	-	-	-	-
	Laninamivir octanoate 40 mg group	56	76.0 (45.4-94.3)	-	-	−11.1 (−32.9 to 13.0)	0.4536
Global phase III study in adults (Study CS8958-A-J301) (reference data)	Laninamivir octanoate 20 mg group	326	85.8 (76.5-92.8)	12.2 (−1.5 to 17.2)	0.1043	-	-
	Laninamivir octanoate 40 mg group	334	73.0 (68.4-80.8)	−0.6 (−9.9 to 6.9)	0.7481	−12.8 (−18.2 to −0.4)	0.0384
	Oseltamivir phosphate group	336	73.6 (68.5-83.3)	-	-	-	-

In the study in patients aged ≤9 years (Study CS8958-A-J302), time to alleviation of symptoms was defined as the time point at which all influenza symptoms (nasal symptoms, cough) improved with body temperature decreased to 37.4°C or ≤36.9°C and remained in that state for ≥21.5 hours .
In the study in patients aged 10 to 19 years (Study CS8958-A-J303) and the study in the global phase III study (Study CS8958-A-J301), time to alleviation of symptoms was defined as the time point at which all influenza symptoms (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough) improved and remained at that state for ≥21.5 hours.
a) Estimated by the Kaplan-Meier method
b) Generalized Wilcoxon test

PMDA considers as follows:
The efficacy of a single dose inhalation of laninamivir octanoate 40 mg in adult patients with influenza virus infection was confirmed [see "4.(ii).B.(1).2).(a) Efficacy of laninamivir octanoate (adults)"]. Taking account of the following points, PMDA concluded that the efficacy of laninamivir octanoate in pediatric patients with influenza virus infection had also been confirmed.

- In the study conducted in patients aged 10 to 19 years (Study CS8958-A-J303), time to alleviation of symptoms tended to be shorter in the laninamivir octanoate 40 mg group than in the laninamivir octanoate 20 mg group, as was the case in adults.

- In the study conducted in patients aged ≤9 years (Study CS8958-A-J302), time to alleviation of symptoms in the laninamivir octanoate 20 mg group was statistically significantly shorter than in the oseltamivir phosphate group, and time to alleviation of symptoms in the laninamivir

octanoate 40 mg group was also shorter, albeit statistically insignificant, although these comparisons were not powered for statistical testing.

Taking account of the following point, PMDA asked the applicant to discuss the reason(s) why the trends in times to alleviation of symptoms in the laninamivir octanoate groups relative to the control group in the study in patients aged ≤9 years (Study CS8958-A-J302) were different from the results of the study in patients aged 10 to 19 years (Study CS8958-A-J303) and the global phase III study (Study CS8958-A-J301).

- In the study conducted in patients aged ≤9 years (Study CS8958-A-J302), in a comparison with the oseltamivir phosphate group, time to alleviation of symptoms was significantly shorter in the laninamivir octanoate 20 mg group, and it tended to be shorter also in the laninamivir octanoate 40 mg group. In contrast, in the global phase III study (Study CS8958-A-J301) in adult patients with influenza virus infection, while all laninamivir octanoate groups were non-inferior to the control group, time to alleviation of symptoms tended to be prolonged in the laninamivir octanoate 20 mg group than in the control group.

The applicant responded as follows:
The sums of the baseline nasal symptom and cough scores (arithmetic mean) were 2.2 to 2.7 in the study in patients aged ≤9 years (Study CS8958-A-J302), 2.8 to 3.1 in the study in patients aged 10 to 19 years (Study CS8958-A-J303), and were 3.0 to 3.1 in the global phase III study (Study CS8958-A-J301), showing a trend toward lower scores with younger patients. Also, the median times from the onset of influenza symptoms to the end of treatment were 18.80 to 19.80 in the study in patients aged ≤9 years (Study CS8958-A-J302) and 19.25 to 21.90 in the study in patients aged 10 to 19 years (Study CS8958-A-J303), whereas those were 24.30 to 25.30 in the global phase III study (Study CS8958-A-J301), showing shorter time in the children than the adults. It is assumed that the child is taken to a clinic by the parent or guardian before symptoms become severe, and this is considered to be a reason for the children's low symptom scores at baseline. When the symptom score is low, time to alleviation of symptoms tends to be shorter.[55] Therefore, it is likely that the difference in baseline symptom scores resulted in the difference in times to alleviation of symptoms among the studies.

Furthermore, symptom rating were performed, based on the signs of the patients, by their parent or guardian in the study in patients aged ≤9 years (Study CS8958-A-J302) while symptoms were rated subjectively by the patients in the study in patients aged 10 to 19 years (Study CS8958-A-J303) and the global phase III study (Study CS8958-A-J301).This may have resulted in scoring discrepancies among the studies. Times to alleviation of symptoms in the global phase III study (Study CS8958-A-J301) were therefore re-calculated based on the definition of time to alleviation of symptoms in the study in patients aged ≤9 years (Study CS8958-A-J302).[56] As a result, the median time to alleviation of symptoms (according to the definition in the study in patients aged ≤9 years) in the global phase III study (Study CS8958-A-J301) was 69.5 hours in the laninamivir octanoate 20 mg group, 61.3 hours in the laninamivir octanoate 40 mg group, and was 63.4 hours in the oseltamivir phosphate group. In the study in patients aged ≤9 years (Study CS8958-A-J302), the median time to alleviation of symptoms was 56.4 hours in the laninamivir octanoate 20 mg group, 55.4 hours in the laninamivir octanoate 40 mg group, and was 87.3 hours in the oseltamivir phosphate group (see the table below). Thus, when the common definition was used in the study in patients aged ≤9 years (Study CS8958-A-J302) and the global phase III study (Study CS8958-

[55] In the global phase III study (Study CS8958-A-J301), the study in patients aged ≤9 years (Study CS8958-A-J302), and the study in patients aged 10 to 19 years (Study CS8958-A-J303), results of Cox regression analyses conducted as secondary analysis of the primary endpoint showed that the total of baseline influenza symptom scores was a covariate that statistically significantly prolonged time to alleviation of symptoms.

[56] A duration until the beginning of a state lasting for ≥21.5 hours with 2 symptoms, a nasal symptom and cough, "resolved" or improved to "mild" and decreased body temperature to ≤37.4°C,

A-J301), there was no significant difference in times to alleviation of symptoms between the laninamivir octanoate dose groups in the 2 studies, except for a trend toward shorter time in the former study than in the latter. Thus, the observed inconsistency in the efficacy of laninamivir octanoate between children and adults in each laninamivir octanoate dose group is considered attributable to the difference in the efficacy of oseltamivir phosphate between these age groups and the difference in the definition of time to alleviation of symptoms.

Time to alleviation of influenza symptoms (according to the definition in the study in patients aged ≤9 years)

Study	Median[a)] (h) (95% CI)		
	Laninamivir octanoate 20 mg group	Laninamivir octanoate 40 mg group	Oseltamivir phosphate group
Global phase III study (definition used in studies in adults)	85.8 (76.5-92.8)	73.0 (68.4-80.8)	73.6 (68.5-83.3)
Global phase III study (definition used in study in patients aged ≤9 years)	69.5 (61.7-76.5)	61.3 (54.3-67.8)	63.4 (54.6-70.2)
Study in patients aged ≤9 years	56.4 (43.7-69.2)	55.4 (46.3-81.3)	87.3 (67.9-129.7)

a) Estimated by the Kaplan-Meier method

PMDA considers as follows:
Regarding the results of the study in patients aged ≤9 years (Study CS8958-A-J302), the following explanation by the applicant are generally acceptable: (a) baseline symptom scores were low and the patients are assumed to have been taken to see a physician by their parent or guardian before the symptoms became severe, and (b) the symptoms were rated, based on the signs of the patients, by their parent or guardian, and the definition of time to alleviation of symptoms was not standardized with other studies enrolling different age groups. These factors contributed to the reduced times to alleviation of symptoms in the laninamivir octanoate groups in this study as compared with the study in patients aged 10 to 19 years (Study CS8958-A-J303) and the global phase III study (Study CS8958-A-J301).

On the other hand, PMDA considered that contributory factors of the inconsistency between the laninamivir octanoate dose groups and the oseltamivir phosphate group observed in the global phase III study (Study CS8958-A-J301) and the study in patients aged ≤9 years (Study CS8958-A-J302), other than the mentioned differences in baseline symptom scores and in the definition of time to alleviation of symptoms, should also be investigated. PMDA therefore asked the applicant to discuss such factors while taking account of the difference in the local exposure to laninamivir octanoate in the lungs between adults and children aged ≤9 years and the difference in NA-inhibitory activity between R-125489 and the active form of oseltamivir.

The applicant responded as follows:
Although the drug concentrations in the target site of the lungs is known neither in children aged ≤9 years nor adults, the characteristics of the inhaler and the result of the PPK analysis suggested that there is no significant difference in the amount of fine particle dose inhaled or absorbed between adults in the global phase III study (Study CS8958-A-J301) and children in the study in patients aged ≤9 years (Study CS8958-A-J302) [see "4.(i).B.(3) Concentration in the plasma and in the target site in the lungs in pediatric patients"].

The values of NA-inhibitory activity (IC_{50}) (minimum–maximum) of R-125489 against A/H1N1 subtype were 0.45 to 4.4 nM in the global phase III study (Study CS8958-A-J301) and 0.81 to 3.6 nM in the study in patients aged ≤9 years (Study CS8958-A-J302). IC_{50} values of the active form

of oseltamivir were 89 to 1500 nM in the global phase III study (Study CS8958-A-J301) and 210 to 1200 nM in the study in patients aged ≤9 years (Study CS8958-A-J302), which were higher than those of laninamivir octanoate in both studies. However, the clinical efficacy of oseltamivir phosphate against A/H1N1 subtype in the global phase III study (Study CS8958-A-J301) appeared to be similar in the Japanese phase II single dose study (Study CS8958-A-J201) which was conducted during the 2007/08 season when H275Y mutant virus was not epidemic. In the Japanese phase II single dose study (Study CS8958-A-J201), IC_{50} values of the active form of oseltamivir against A/H1N1 were 0.25 to 4.6 nM except in 4 strains (out of 269 strains) that showed IC_{50} values of 670 to770 nM.

In contrast, published literature suggested that the clinical efficacy of oseltamivir phosphate against A/H1N1 subtype virus with H275Y mutation is reduced in children as compared with adults.[57] Acquired immunity becomes mature after receiving repeated stimulation from different antigens and children therefore is considered to have relatively immature immunity. In the literature, the difference in the efficacy of oseltamivir phosphate between adults and children was assumed to be due to different immune responses in adults and children or the insufficient dose of oseltamivir phosphate in children.

While IC_{50} values of the active form of oseltamivir against A/H1N1 subtype were high in both the global phase III study (Study CS8958-A-J301) and the study in patients aged ≤9 years (Study CS8958-A-J302), the clinical efficacy of oseltamivir phosphate was maintained in adults and reduced in children. This is thought to be a cause of inconsistent trends between the 2 studies in the comparison of the efficacy between the laninamivir octanoate groups and oseltamivir phosphate group.

Based on the following observations, PMDA considers that the reduced clinical efficacy of oseltamivir phosphate particularly in children was a possible cause of the inconsistent trends between the global phase III study (Study CS8958-A-J301) and the study in patients aged ≤9 years (Study CS8958-A-J302) in the comparison of the efficacy between the laninamivir octanoate groups and the oseltamivir phosphate group: (a) the published literature (*J Infect.* 2009;59(3):207-12, *Clin Infect Dis.* 2009;49(12):1828-35) on an observational study through clinical practice, not on a clinical study, revealed reduced clinical efficacy of oseltamivir phosphate particularly significant in children in a comparison between the 2008/09 season and the 2007/08 season, (b) time to alleviation of symptoms was longer in children aged ≤9 years in the oseltamivir phosphate group than in adults even after the definition of time to alleviation of influenza symptoms in the 2 studies had been standardized.

However, as discussed in "4.(ii).B.(1).2).(a) Efficacy of laninamivir octanoate (adults)," whether or not the efficacy of oseltamivir phosphate in adults was maintained regardless of the presence or absence of H275Y mutation is unclear. In addition, the drug concentrations in target sites in the lungs were unknown in both adults and children aged ≤9 years. Therefore, the possibility cannot be excluded that the difference between the global phase III study (Study CS8958-A-J301) and the study in patients aged ≤9 years (Study CS8958-A-J302) in the local exposure to laninamivir octanoate in the lungs was a cause of the inconsistency between the 2 studies in the comparison of the efficacy between the laninamivir octanoate groups and the oseltamivir phosphate group.

PMDA also conducted the following review concerning the dose of laninamivir octanoate.

The result of the study in patients aged ≤9 years (Study CS8958-A-J302) showed that laninamivir octanoate at a dose higher than 40 mg is not expected to increase the efficacy in children. In contrast, in the global phase III study (Study CS8958-A-J301) in adults, a dose-response

[57] *J Infect.* 2009;59(3):207-12.

relationship was observed between the laninamivir octanoate 20 mg and 40 mg groups. This finding, along with the earlier discussion on the difference in efficacy between children and adults, suggested that higher efficacy may be achieved in adults at a dose higher than 40 mg. Therefore, PMDA asked the applicant's view on the need for investigation of the efficacy in adults at a dose higher than 40 mg.

The applicant responded as follows:
In the global phase III study (Study CS8958-A-J301) conducted in the 2008/09 season when an oseltamivir-resistant H275Y mutant virus was epidemic, the clinical efficacy of oseltamivir phosphate was similar to that in the Japanese phase II single dose study (Study CS8958-A-J201) conducted in the 2007/08 season. This suggests that laninamivir octanoate 40 mg, for which efficacy was verified in the global phase III study (Study CS8958-A-J301) using oseltamivir phosphate as control, is clinically effective against the H275Y mutant virus. Also, R-125489 had favorable inhibitory activity (0.45-4.4 nM) against NA of the H275Y mutant virus isolated in the global phase III study (Study CS8958-A-J301) with no cross resistance. These results suggest that laninamivir octanoate 40 mg should remain clinically effective in possible future outbreaks of the H275Y mutant virus. Therefore, the applicant considers the investigation of doses higher than 40 mg for clinical use is not necessary.

PMDA considers as follows:
From the point of view of the optimum dose, higher doses of laninamivir octanoate should preferably be studied for use in adults. However, the submitted study results have demonstrated the clinical efficacy of laninamivir octanoate at the dose of 40 mg. Also, as explained by the applicant, laninamivir octanoate has a favorable NA-inhibitory activity against the H275Y mutant virus and is expected to be clinically effective even in the event of an outbreak of the H275Y mutant virus in the future. Therefore, there is no urgent need for further studies on the efficacy or safety of laninamivir octanoate at doses higher than 40 mg for now.

The above conclusion of PMDA is going to be discussed at the Expert Discussion.

4.(ii).B.(1).3) Secondary evaluation of efficacy

(a) Efficacy by type of influenza virus

In the global phase III study (Study CS8958-A-J301) and the study in patients aged ≤9 years (Study CS8958-A-J302), the results of analyses of time to alleviation of symptoms by viral type and subtype were as shown below. In the global phase III study (Study CS8958-A-J301), a subgroup analysis of influenza B virus was not performed because there were only 3 eligible subjects.

Time to alleviation of symptoms in global phase III study (Study CS8958-A-J301) (by viral type and subtype) (FAS)

Influenza A/H1N1 virus infection			
	Laninamivir octanoate 20 mg group N = 215	Laninamivir octanoate 40 mg group N = 218	Oseltamivir phosphate group N = 212
Median (hr) [a)]	82.9	74.0	77.5
95% CI	73.0-91.8	69.3-82.0	70.2-93.8
Influenza A/H3N2 virus infection			
	Laninamivir octanoate 20 mg group N = 102	Laninamivir octanoate 40 mg group N = 108	Oseltamivir phosphate group N = 112
Median (hr) [a)]	91.2	72.5	67.5
95% CI	71.6-116.8	57.8-88.6	53.5-76.3

a) Estimated by the Kaplan-Meier method

Time to alleviation of symptoms in study in patients aged ≤9 years (Study CS8958-A-J302) (by viral type and subtype) (FAS)

Influenza A/H1N1 subtype virus infection			
	Laninamivir octanoate 20 mg group N = 40	Laninamivir octanoate 40 mg group N = 40	Oseltamivir phosphate group N = 32
Median (hr) [a)]	44.3	49.6	110.5
95% CI	24.3-58.9	39.7-62.1	68.8-141.9
Influenza A/H3N2 subtype virus infection			
	Laninamivir octanoate 20 mg group N = 12	Laninamivir octanoate 40 mg group N = 11	Oseltamivir phosphate group N = 16
Median (hr) [a)]	70.4	88.6	44.3
95% CI	30.3-110.9	43.5-114.9	22.9-82.1
Influenza B virus infection			
	Laninamivir octanoate 20 mg group N = 9	Laninamivir octanoate 40 mg group N = 10	Oseltamivir phosphate group N = 10
Median (hr) [a)]	83.5	77.6	127.8
95% CI	66.6-107.8	51.8-95.8	77.1-165.3

a) Estimated by the Kaplan-Meier method

i) Influenza A virus infection

The applicant explained the efficacy of laninamivir octanoate against the type A virus as follows: The Kaplan-Meier plotting of time to alleviation of symptoms in patients with influenza A virus infection of A/H1N1 subtype in the global phase III study (Study CS8958-A-J301) in adults showed that patients in the laninamivir octanoate 20 mg group, the laninamivir octanoate 40 mg group, and the oseltamivir phosphate group recovered from the symptoms with similar time courses, with the median times to alleviation of symptoms being 82.9 hours, 74.0 hours, and 77.5 hours, respectively. The difference (95% CI) in the median time from the oseltamivir phosphate group was 5.4 (−10.7 to 11.6) hours in the laninamivir octanoate 20 mg group and −3.5 (−15.2 to 6.8) hours in the laninamivir octanoate 40 mg group, showing no significant difference in times to alleviation of symptoms between the laninamivir octanoate groups and the oseltamivir phosphate group. IC_{50} values of R-125489, the active form of laninamivir octanoate, against NA activity of isolated A/H1N1 subtype strains were 0.45 to 4.40 nM, whereas IC_{50} values of the active form of oseltamivir was 89 to 1500 nM.

The global phase III study (Study CS8958-A-J301) was conducted in the 2008/09 season when H275Y mutant virus was epidemic, and this study also had patients with H275Y mutation, which accounted for 99.7% of patients (644 of 646) with influenza A/H1N1 virus infection. While scant data on the clinical efficacy of oseltamivir phosphate against oseltamivir-resistant strains showed reduced efficacy in pediatric patients, there was a report on a certain extent of the efficacy of oseltamivir phosphate observed in adults with minimal impact of resistance to oseltamivir.[58] The result of the global phase III study (Study CS8958-A-J301) was also considered to have suggested that oseltamivir resistance of influenza virus did not significantly affect the clinical efficacy of oseltamivir phosphate in adult patients.

The result of the study in patients aged ≤9 years (Study CS8958-A-J302) showed that patients in the laninamivir octanoate 20 mg and 40 mg groups tended to recover from influenza A/H1N1 virus infection earlier than patients in the oseltamivir phosphate group, as assessed from Kaplan-Meier plotting of times to alleviation of symptoms (criterion for body temperature, ≤37.4°C), with the median time to alleviation of symptoms being 44.3 hours in the laninamivir octanoate 20 mg group, 49.6 hours in the laninamivir octanoate 40 mg group, and 110.5 hours in the oseltamivir phosphate group. The difference (95% CI) in the median time to alleviation of symptoms as

[58] *J. infect.* 2009;59(3):207-12

compared with the oseltamivir phosphate group was −66.2 (−81.2 to −18.5) hours in the laninamivir octanoate 20 mg group and was −60.9 (−71.0 to −10.2) hours in the laninamivir octanoate 40 mg group, showing that both results were significantly shorter than the result of the oseltamivir phosphate group (P = 0.0012 [laninamivir octanoate 20 mg group], P = 0.0079 [laninamivir 40 mg group]). On Day 3, the viral titer was below the detection limit in approximately half of subjects in all treatment groups, resulting in showing the same median value across the treatment groups; the arithmetic means also showed a similar trend. The percentage of subjects with the viral titer below the detection limit was similar among treatment groups on Day 3, whereas, on Day 6, it was significantly higher in the laninamivir octanoate 20 mg group than in the oseltamivir phosphate group (P = 0.0009); a similar trend was observed in the laninamivir octanoate 40 mg group as well. IC_{50} values of the active form of oseltamivir against NA activity of isolated A/H1N1 subtype virus strains were 210 to 1200 nM, whereas IC_{50} value of R-125489 were 0.81 to 3.60 nM.

In adult patients with A/H3N2 subtype infection (102 patients in the laninamivir octanoate 20 mg group, 108 patients in the laninamivir octanoate 40 mg group, 112 patients in the oseltamivir phosphate group), the median time to alleviation of symptoms was 91.2 hours in the laninamivir octanoate 20 mg group, 72.5 hours in the laninamivir octanoate 40 mg group, and was 67.5 hours in the oseltamivir phosphate group. The difference (95% CI) in the median time to alleviation of symptoms as compared with the oseltamivir phosphate group was 23.7 (3.4-38.7) hours in the laninamivir octanoate 20 mg group and was 5.0 (−7.3 to 19.8) hours in the laninamivir octanoate 40 mg group, showing a significantly longer time to alleviation of symptoms in the laninamivir octanoate 20 mg group than in the oseltamivir phosphate group (P = 0.0141). Thus, laninamivir octanoate 20 mg was not sufficiently effective against A/H3N2 subtype as compared with oseltamivir phosphate, whereas laninamivir octanoate 40 mg was considered to be effective against A/H3N2 subtype as well.

In pediatric patients with A/H3N2 subtype infection (12 patients in the laninamivir octanoate 20 mg group, 11 patients in the laninamivir octanoate 40 mg group, 16 patients in the oseltamivir phosphate group), time to alleviation of symptoms was 70.4 hours in the laninamivir octanoate 20 mg group, 88.6 hours in the laninamivir octanoate 40 mg group, and was 44.3 hours in the oseltamivir phosphate group. The difference (95% CI) in the median time as compared with the oseltamivir phosphate group was 26.2 (−24.8 to 51.2) hours in the laninamivir octanoate 20 mg group and 44.4 (−14.8 to 68.5) hours in the laninamivir octanoate 40 mg group, showing a trend toward longer time to alleviation of symptoms in both laninamivir octanoate groups than in the oseltamivir phosphate group.

Thus, in adults, although laninamivir octanoate was not sufficiently effective against A/H3N2 subtype at the dose of 20 mg, it was considered to be effective against both A/H1N1 and A/H3N2 subtypes at the dose of 40 mg. In children, laninamivir octanoate demonstrated its efficacy against A/H1N1 subtype at both the 20 mg and 40 mg doses, whereas the possibility of reduced efficacy of laninamivir octanoate against A/H3N2 subtype was suggested, though in a small number of subjects.

PMDA considers as follows:
Taking account of the discussion in "4.(ii).B.(1).2).(a) Efficacy of laninamivir octanoate (adults)," although the possibility cannot be completely excluded that the efficacy of the control oseltamivir phosphate against A/H1N1 subtype is attenuated by H275Y mutation, laninamivir octanoate 40 mg is expected to be clinically effective against A/H1N1 subtype viruses, including H275Y mutant strain. In children, time to alleviation of symptoms was reduced to a significantly greater extent by laninamivir octanoate than by oseltamivir phosphate as far as in the result of the study in patients aged ≤9 years (Study CS8958-A-J302), suggesting that laninamivir octanoate is effective against influenza A/H1N1 virus infection in children. The close monitoring of trends in

the emergence of laninamivir octanoate-resistant virus strains should be continued after the market launch.

In the study in patients aged ≤9 years (Study CS8958-A-J302), unlike A/H1N1 subtype and type B viruses, A/H3N2 subtype virus tended to prolong time to alleviation of symptoms in both laninamivir octanoate groups as compared with the oseltamivir phosphate group. PMDA asked the applicant to discuss the reason(s) for this tendency.

The applicant responded as follows:
Patients in the both laninamivir octanoate groups, regardless of viral type or subtype, tended to have higher body temperature at baseline as compared with patients in the oseltamivir phosphate group. The laninamivir octanoate groups included patients with high body temperature exhibiting relatively severe symptoms, and this could contribute to the prolonged times to alleviation of symptoms of the groups, although the number of subjects was too small for adequate discussion. A report[59] comparing the clinical efficacy between oseltamivir phosphate and zanamivir hydrate over 5 seasons from 2003/04 through 2007/08 states that "both were equally effective against A/H1N1 subtype, but oseltamivir phosphate was significantly superior in shortening the febrile period of patients with A/H3N2 subtype influenza. This suggests that oseltamivir phosphate is more effective than zanamivir hydrate against A/H3N2 subtype."

Thus, the large percentage of patients with relatively severe symptoms accounted for the laninamivir octanoate groups and the superior efficacy of oseltamivir phosphate against A/H3N2 subtype may have led to the prolonged times to alleviation of symptoms in both laninamivir octanoate groups as compared with the oseltamivir phosphate group.

PMDA considers as follows:
In the study in patients aged ≤9 years (Study CS8958-A-J302), patients with relatively severe symptoms were not necessarily included in the laninamivir octanoate groups according to their total influenza symptom scores at baseline. Thus, this does not seem a plausible reason for the trend toward prolonged times to alleviation of symptoms in the laninamivir octanoate groups as compared with the oseltamivir phosphate group. While there is a report suggesting the superiority of oseltamivir phosphate to zanamivir hydrate in efficacy against A/H3N2 subtype (*Clin Infect Dis.* 2009;48:996-997), another report points out similar efficacy of oseltamivir phosphate and zanamivir hydrate against A/H1N1 and A/H3N2 subtypes and type B based on a study of pediatric patients with influenza virus infection by viral type and subtype (*Clin Infect Dis*. 2008;47:339-345). Therefore, the efficacy of oseltamivir phosphate against A/H3N2 subtype is considered not to have been established. Given the small number of subjects studied, the results of viral type- or subtype-based efficacy evaluations of laninamivir octanoate should be interpreted carefully.

The available study results indicate that laninamivir octanoate 40 mg is expected to be effective against A/H3N2 subtype nearly equivalent to oseltamivir phosphate in adults. In children, however, it is not certain that laninamivir octanoate 40 mg is equally effective to oseltamivir phosphate against A/H3N2 subtype. Also, laninamivir octanoate 40 mg did not show the trend toward shorter time to alleviation of symptoms than laninamivir octanoate 20 mg and failed to suggest a dose-dependent relationship. Thus, the possibility of reduced efficacy of laninamivir octanoate against A/H3N2 subtype in pediatric patients as compared with oseltamivir phosphate still remains, and there is no sufficient proof of efficacy because of the limited number of subjects studied. Therefore, information collection should be continued after the market launch on the efficacy of laninamivir octanoate by viral type and subtype, including the efficacy in pediatric patients with A/H3N2 subtype virus infection.

[59] *Clin Infect Dis*. 2009;48(7):996-7

ii) Influenza B virus infection

The applicant explained the efficacy of laninamivir octanoate against influenza B virus infection as follows:

The efficacy of laninamivir octanoate in adults was not evaluated in the global phase III study (Study CS8958-A-J301) due to only 3 patients with influenza B virus infection. In the phase II study (Study CS8958-A-A202) in Taiwan, in contrast, there were 33 subjects with a diagnosis of influenza B virus infection (12 patients in the laninamivir octanoate 10 mg group, 12 patients in the laninamivir octanoate 20 mg group, 9 patients in the placebo group), and a Kaplan-Meier plotting of time to alleviation of symptoms of influenza B virus infection showed earlier recovery in the laninamivir octanoate groups than in the placebo group. The median time to alleviation of symptoms was 62.4 hour in the laninamivir octanoate 10 mg group, 58.4 hours in the laninamivir octanoate 20 mg group, and was 112.8 hours in the placebo group. The inhibitory activity (IC_{50} values) of R-125489 and that of the active form of oseltamivir against NA of influenza B virus strains isolated in all clinical studies conducted in patients were 9.0 to 29 nM and 8.2 to 53 nM, respectively, showing similar inhibitory activities. Based on these results, the applicant considered that a single dose of laninamivir 40 mg is effective against influenza B virus infection.

The efficacy of laninamivir octanoate in children in a Kaplan-Meier plotting of time to alleviation of symptoms of influenza B virus infection in the study in patients aged ≤9 years (Study CS8958-A-J302) showed a trend toward earlier recovery in the laninamivir octanoate groups as compared with the oseltamivir phosphate group, with the median times to alleviation of symptoms being 83.5 hours in the laninamivir octanoate 20 mg group, 77.6 hours in the laninamivir octanoate 40 mg group, and 127.8 hours in the oseltamivir phosphate group. The difference (95% CI) in the median times to alleviation of symptoms relative to the oseltamivir phosphate group was −44.3 (−93.8 to 36.1) hours in the laninamivir octanoate 20 mg group and −50.2 (−104.4 to 10.4) hours in the laninamivir octanoate 40 mg group, showing a trend toward shorter times to alleviation of symptoms in the laninamivir octanoate groups as compared with the oseltamivir phosphate group. The median times to for body temperature to return to ≤37.4°C were similar between the laninamivir octanoate groups and the oseltamivir phosphate group. The median and arithmetic mean of viral titers on Day 3 were lower in the laninamivir octanoate groups than in the oseltamivir phosphate group. The percentages of subjects with viral titer below the detection limit were similar among the treatment groups both on Day 3 (22.2% in the laninamivir 20 mg group, 30.0% in the laninamivir octanoate 40 mg group, 10.0% in the oseltamivir phosphate group) and on Day 6 (66.7% in the laninamivir octanoate 20 mg group, 70.0% in the laninamivir octanoate 40 mg group, 60.0% in the oseltamivir phosphate group). IC_{50} values of the active form of oseltamivir against NA activity of isolated influenza B virus strains were 12 to 53 nM, and those of R-125489 were 11 to 26 nM. Thus, there were no isolated type B virus strains that had high IC_{50} values to the active form of oseltamivir or R-125489. These data suggested the possibility that laninamivir octanoate is possibly more effective than oseltamivir phosphate against influenza B virus infection in children, though in a small number of subjects.

PMDA considers as follows:

According to the applicant's explanation, in clinical studies in adults and in children, time to alleviation of symptoms tended to be shorter in the laninamivir octanoate groups as compared with the placebo group and the oseltamivir phosphate group. The explanation is acceptable, and laninamivir octanoate is expected to be effective against influenza B virus infection. However, since only limited number of patients with influenza B virus infection were enrolled in clinical studies, information on the efficacy of laninamivir octanoate for the treatment of influenza B virus infection should be further collected after the market launch.

(b) Efficacy by time of symptom onset

The applicant explained the efficacy of laninamivir octanoate against influenza virus infection by time of symptom onset (the time from the onset of influenza symptoms to the end of the treatment with laninamivir octanoate) as follows:

In the global phase III study (Study CS8958-A-J301), the primary endpoint of time to alleviation of symptoms was analyzed and stratified by time from the onset of influenza symptoms to the end of the treatment with laninamivir octanoate. Of patients with the time from the onset of symptoms to the end of the treatment with laninamivir octanoate of <24 hours, those in the laninamivir octanoate 20 mg group were found to have significantly prolonged time to alleviation of symptoms as compared with those in the oseltamivir phosphate group ($P = 0.0097 < 0.01$). Of patients with the time from symptom onset to the end of treatment of ≥24 hours, on the other hand, those in the laninamivir octanoate 40 mg group were revealed to have significantly shorter time to alleviation of symptoms ($P = 0.0373 < 0.05$). The patients in the laninamivir octanoate 40 mg group, regardless of whether their time from symptom onset to the end of treatment was <24 hours or ≥24 hours, did not show significantly prolonged time to alleviation of symptoms as compared with those in the oseltamivir phosphate group.

Time to alleviation of symptom (analysis stratified by the time from the onset of influenza to the end of treatment, FAS)

Time interval from the onset of influenza to the end of treatment	Parameter		Laninamivir octanoate 20 mg group	Laninamivir octanoate 40 mg group	Oseltamivir phosphate group
All subjects	Number of subjects		326	334	336
	Median (hr) (95% CI)		85.8 (76.5-92.8)	73.0 (68.4-80.8)	73.6 (68.5-83.3)
<24 hours	Number of subjects		151	159	147
	Median (hr) (95% CI)		89.5 (71.4-99.3)	76.2 (67.1-85.3)	67.8 (57.0-73.6)
≥24 hours	Number of subjects		175	175	189
	Median (hr) (95% CI)		84.7 (75.3-92.7)	71.4 (65.5-75.7)	79.7 (72.1-93.1)
≥36 hours	Number of subjects		20	15	25
	Median (hr) (95% CI)		74.6 (66.3-104.8)	67.7 (30.8-127.7)	77.9 (50.3-107.9)

Median value was estimated by the Kaplan-Meier method

The maximum time from the onset of influenza symptoms to the end of treatment was 39.8 hours in the laninamivir octanoate 20 mg group, 46.8 hours in the laninamivir octanoate 40 mg group, and was 40.3 hours in the oseltamivir phosphate group. In the subgroup of the mentioned time from the onset of influenza symptoms to the end of treatment of ≥36 hours, both time to alleviation of symptoms and time for body temperature to return to normal shown in Kaplan-Meier plotting were similar to those observed in the entire study population despite a limited number of subjects in the subgroup.

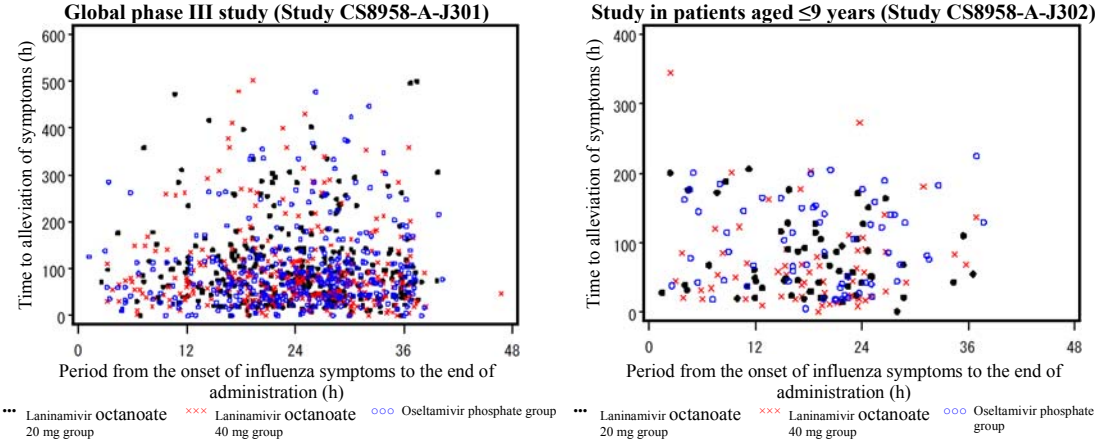
PMDA asked the applicant to explain whether or not the efficacy of laninamivir octanoate varies depending on the time from the onset of influenza symptoms to the treatment with laninamivir octanoate and a view on the maximum hours of the mentioned time that ensures the efficacy of laninamivir octanoate.

The applicant responded as follows:
Scatter diagrams below show the time from the onset of influenza symptoms to the end of treatment and times to alleviation of symptoms based on the results of the global phase III study (Study CS8958-A-J301) in adult patients with influenza virus infection and the study in patients aged ≤9 years (Study CS8958-A-J302) in pediatric patients with influenza virus infection. Neither in the global phase III study (Study CS8958-A-J301) nor in the study in patients aged ≤9 years (Study CS8958-A-J302), a clear relationship was not observed between the time from the onset of symptoms to the end of treatment and time to alleviation of symptoms. Therefore, the efficacy of laninamivir octanoate is unlikely to be affected by the time from the onset of symptoms to the end of treatment, either in adults or in children.

In clinical studies of laninamivir octanoate for the treatment of influenza virus infection, an inclusion criterion required the subject to be enrolled within 26 hours after the onset of symptoms, and therefore there were only a small number of subjects who turned out to have the time from the onset of symptoms to the end of treatment of ≥36 hours. Nevertheless, in the global phase III study (Study CS8958-A-J301), times to alleviation of symptoms were similar between the subgroup with the time from the onset of symptoms to the end of treatment of ≥36 hours (maximum 46.8 hours) and the entire subject population. In general, antiviral drug therapy for influenza should preferably be started as early as possible before the peak of viral proliferation, which is thought to be approximately 48 hours.

Laninamivir octanoate was confirmed to be effective even in patients with the time from the onset of symptoms to the end of treatment of ≥36 hours in the clinical studies, the efficacy of laninamivir octanoate is assumed to be ensured when administered at least within 48 hours after the onset of symptoms. There are no data that support the efficacy of the drug when administered ≥48 hours after the onset of symptoms, and this information is to be added in the package insert.

Scatter diagrams of period from the onset of influenza symptoms to the end of treatment versus time to alleviation of symptoms



PMDA considers as follows:
In the global phase III study (Study CS8958-A-J301) and the study in patients aged ≤9 years (Study CS8958-A-J302), the time from the onset of symptoms to the end of treatment did not affect the efficacy of laninamivir octanoate in patients with the said time of ≤36 hours. Despite the absence of a significant difference in the efficacy between the subgroup of patients with the said time of ≤36 hours and the entire subject population, these findings in the subgroup with a small number of patients do not seem to plausibly justify the applicant's opinion that the efficacy of laninamivir octanoate is ensured if administered within 48 hours after onset. Given the mechanism of action of laninamivir octanoate against influenza virus infection, the drug should

be administered as early as possible. The package insert should alert to the lack of experience in the administration of laninamivir octanoate ≥36 hours after the onset of symptoms.

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

4.(ii).B.(1).4) Other

4.(ii).B.(1).4).(a) Resistance to laninamivir octanoate

The applicant explained the emergence of resistance to laninamivir octanoate as follows:
In clinical studies of laninamivir octanoate, the inhibitory activities (IC_{50}) of R-125489, the active form of laninamivir octanoate, and the active form of oseltamivir against NA of influenza virus isolates from patients were compared between pre- and post-treatment with the study drug to investigate possible emergence of influenza virus strains resistant to laninamivir octanoate.

In the phase II single dose study (Study CS8958-A-J201) conducted in Japan during the 2007/08 season, virus isolates obtained from 6 subjects (1 in the laninamivir octanoate 5 mg group, 1 in the laninamivir octanoate 10 mg group, and the laninamivir octanoate 20 mg group, 3 in the oseltamivir phosphate group) showed the post-treatment IC_{50} of the active form of oseltamivir that was ≥2-fold (maximum 3.9-fold) the pre-treatment value. Pre- and post-treatment comparisons of the amino acid sequences of these samples were performed by base sequencing of NA gene and suspected I54T mutation and D151N mutation in 1 sample each were identified. The 2 samples were obtained from subjects in the oseltamivir phosphate group. The amino acid sequence of the remaining 4 post-treatment samples were identical to those of the pre-treatment samples, and no mutations were identified. In the virus isolates with a suspected mutation in the amino acid sequence that constitutes the enzyme active center of NA, IC_{50} values of the active form of oseltamivir were ≤4.0 nM, and this did not strongly suggested the emergence of resistance after the treatment. There were no subjects with post-treatment IC_{50} of R-125489 of ≥2-fold pre-treatment value. Considering a change of <4-fold in IC_{50} is not a consequence of acquired resistance, virus extraction was performed on the sample with post-treatment IC_{50} of ≥4-fold pre-treatment value in subsequent studies. In the phase II study (Study CS8958-A-A202) in Taiwan, there were no virus isolates that showed a ≥4-fold increase in IC_{50} of R-125489 or the active form of oseltamivir after the treatment with the study drug.

In 6 clinical studies including the global phase III study (Study CS8958-A-J301) conducted during the 2008/09 season, the Japanese phase II multiple dose study (Study CS8958-A-J203), the study to compare inhalers (Study CS8958-A-J304), the study in patients aged ≤9 years (Study CS8958-A-J302), the study in patients aged 10 to 19 years (Study CS8958-A-J303), and the pediatric PK study (Study CS8958-A-J204), there were no virus isolates from any subjects that showed a ≥4-fold increase in IC_{50} of the active form of laninamivir octanoate (R-125489) or the active form of oseltamivir.

PMDA considers as follows:
According to the applicant's explanation, there was no particular concern about the emergence of a virus strain resistant to laninamivir octanoate for now. However, given the possible emergence of laninamivir octanoate-resistant virus strains in future, a further survey should be conducted on over-time trends of virus resistance by viral type over the years after the market launch.

4.(ii).B.(2) Safety

4.(ii).B.(2).1) Safety of laninamivir octanoate

(a) Adults

The applicant explained the safety of laninamivir octanoate in adults as follows:
In the 5 clinical studies conducted in adult patients with influenza virus infection, the incidences of adverse events and adverse drug reactions were as shown in the following table. In terms of laninamivir octanoate, results in only the 20 and 40 mg single-dose groups are shown.

Adverse events and adverse drug reactions with an incidence of ≥2% in any group (pooled analysis of 5 phase II/III studies in adult patients with influenza virus infection)

System organ class	Preferred term	Adverse events				Adverse drug reactions			
		Laninamivir octanoate 20 mg group (N = 463)	Laninamivir octanoate 40 mg group (N = 519)	Oseltamivir phosphate group (N = 513)	Placebo group (N = 62)	Laninamivir octanoate 20 mg group (N = 463)	Laninamivir octanoate 40 mg group (N = 519)	Oseltamivir phosphate group (N = 513)	Placebo group (N = 62)
		No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)	No. of patients with even (%)	No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)
All events		128 (27.6)	114 (22.0)	139 (27.1)	14 (22.6)	51 (11.0)	53 (10.2)	69 (13.5)	3 (4.8)
Gastrointestinal disorders	Diarrhoea	24 (5.2)	35 (6.7)	40 (7.8)	3 (4.8)	19 (4.1)	30 (5.8)	36 (7.0)	1 (1.6)
	Nausea	8 (1.7)	5 (1.0)	11 (2.1)	0 (0.0)	4 (0.9)	3 (0.6)	7 (1.4)	0 (0.0)
	Vomiting	2 (0.4)	1 (0.2)	11 (2.1)	0 (0.0)	1 (0.2)	1 (0.2)	8 (1.6)	0 (0.0)
Infections and infestations	Nasopharyngitis	4 (0.9)	14 (2.7)	12 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	ALT increased	7 (1.5)	5 (1.0)	3 (0.6)	2 (3.2)	7 (1.5)	3 (0.6)	3 (0.6)	0 (0.0)
	AST increased	5 (1.1)	1 (0.2)	1 (0.2)	2 (3.2)	5 (1.1)	0 (0.0)	1 (0.2)	0 (0.0)

Incidence (%): Number of patients with event / patients evaluated × 100

In adult patients with influenza virus infection who were treated with a single dose of laninamivir octanoate, the incidence of adverse events was 26.6% (21 of 79 patients) in the laninamivir octanoate 5 mg group, 30.5% (43 of 141 patients) in the laninamivir octanoate 10 mg group, 27.6% (128 of 463 patients) in the laninamivir octanoate 20 mg group, and was 22.0% (114 of 519 patients) in the laninamivir octanoate 40 mg group, showing no dose-dependent increase in the overall incidence of adverse events or the incidences of any specific adverse events. The incidence of adverse events in each laninamivir octanoate group were similar to those in the oseltamivir phosphate group. In adult patients with influenza virus infection, the incidence of dizziness was higher in the laninamivir octanoate groups than in the oseltamivir phosphate group (1.0% [13 of 1295 patients] in the laninamivir octanoate group, 0.0% [0 of 513 patients] in the oseltamivir phosphate group). Dizziness that occurred in the laninamivir octanoate groups was mild in 10 patients and moderate in 3 patients, which were all confirmed to have resolved. There were no serious adverse events or adverse drug reactions in the laninamivir octanoate groups.

PMDA considers the safety of laninamivir octanoate in adults as follows:
There were no serious adverse events in the laninamivir octanoate groups, and the most common adverse event was diarrhoea, the incidence of which was similar to that in the oseltamivir phosphate group. Also, in the laninamivir octanoate groups, there were no adverse events with an obviously higher incidence than the oseltamivir phosphate group. Therefore, laninamivir octanoate is considered to have no particular safety problem. However, dizziness was observed only in the laninamivir octanoate groups, and this suggests that the adverse event may be unique to laninamivir octanoate. Therefore, information on adverse events should be further collected after the market launch.

(b) Children

The applicant explained the safety of laninamivir octanoate in children as follows:
In the 3 clinical studies of laninamivir octanoate in pediatric patients with influenza virus infection, the incidences of adverse events and adverse drug reactions were as shown in the following table. In terms of laninamivir octanoate groups, results only in the 20 and 40 mg single-dose groups are shown.

Adverse events and adverse drug reactions with an incidence of ≥2% in any group (pooled analysis of 3 phase II/III studies in pediatric patients with influenza virus infection)

System Organ Class	Preferred term	Adverse events			Adverse drug reactions		
		Laninamivir octanoate 20 mg group (N = 134)	Laninamivir octanoate 40 mg group (N = 131)	Oseltamivir phosphate group (N = 62)	Laninamivir octanoate 20 mg group (N = 134)	Laninamivir octanoate 40 mg group (N = 131)	Oseltamivir phosphate group (N = 62)
		No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)
All events		41 (30.6)	33 (25.2)	24 (38.7)	7 (5.2)	7 (5.3)	4 (6.5)
Gastrointestinal disorders	Diarrhoea	7 (5.2)	4 (3.1)	1 (1.6)	5 (3.7)	2 (1.5)	1 (1.6)
	Stomatitis	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Vomiting	3 (2.2)	2 (1.5)	4 (6.5)	2 (1.5)	1 (0.8)	2 (3.2)
General disorders and administration site conditions	Pyrexia	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	Bronchitis	4 (3.0)	2 (1.5)	4 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Gastroenteritis	6 (4.5)	2 (1.5)	2 (3.2)	0 (0.0)	1 (0.8)	0 (0.0)
	Influenza	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Nasopharyngitis	1 (0.7)	3 (2.3)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Sinusitis	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Epistaxis	2 (1.5)	2 (1.5)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Upper respiratory tract inflammation	5 (3.7)	7 (5.3)	4 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)

Incidence (%): Number of patients with event / patients evaluated × 100

In pediatric patients with influenza virus infection who were treated with a single dose of laninamivir octanoate, the incidence of adverse events was 30.6% (41 of 134 patients) in the laninamivir octanoate 20 mg group and 25.2% (33 of 131 patients) in the laninamivir octanoate 40 mg group. Adverse events such as eczema and rash were not observed in the laninamivir octanoate 20 mg group, while they were observed in 3.1% (4 of 131 patients) in the laninamivir octanoate 40 mg group (eczema and rash in 2 patients each). They were all mild or moderate in severity, and the causal relationship of the events with the study drug was ruled out. There were no adverse events that increased in a dose-dependent manner.

In both adults and children, the incidences of adverse events were similar between the patients with influenza virus infection who were treated with laninamivir octanoate and those who were treated with oseltamivir phosphate. The incidence of adverse events in the laninamivir octanoate group was 25.1% (325 of 1295 patients) in adults and was 27.9% (77 of 276 patients) in children, showing no significant difference between the 2 age groups. In comparisons of respective adverse events (adults, children), ALT increased (1.0% [13 patients], 0.7% [2 patients]) and dizziness (1.0% [13 patients], 0% [0 patient]) were observed more frequently in adults than in children. On the other hand, pyrexia (0.3% [4 patients], 1.1% [3 patients]), bronchitis (0.8% [10 patients], 2.2% [6 patients]), gastroenteritis (0.7% [9 patients], 2.9% [8 patients]), delirium (0% [0 patients], 1.1% [3 patients]), abnormal behaviour (0% [0 patients]), 1.1% [3 patients]), epistaxis (0%, 1.4% [4 patients]), and upper respiratory tract inflammation (0% [0 patients], 4.3% [12 patients]) were observed more frequently in children than in adults. None of these adverse events were serious, and they did not show increases in a dose-dependent manner. The profile of adverse events in the oseltamivir phosphate group was similar to that observed in the laninamivir octanoate groups, both in adults and in children. These adverse events were observed more frequently in children than in adults but were considered not to pose any particular safety concern.

In a comparison of common adverse events in children between the laninamivir octanoate group and the oseltamivir phosphate group, diarrhoea (4.3% [12 patients] in the laninamivir octanoate group, 1.6% [1 subject] in the oseltamivir phosphate group) was observed more frequently in the

laninamivir octanoate group, while vomiting (1.8% [5 patients], 6.5% [4 patients]) and bronchitis (2.2% [6 patients], 6.5% [4 patients]) were observed more frequently in the oseltamivir phosphate group. Diarrhoea was observed more frequently in the laninamivir octanoate group than in the oseltamivir phosphate group, and did not show an increase in a dose-dependent manner. Neither serious adverse events nor serious adverse drug reactions were observed in the laninamivir octanoate group.

PMDA considers the safety of laninamivir octanoate in children as follows:
The most frequent adverse event in children treated with laninamivir octanoate was diarrhoea. Although the incidence was higher in the laninamivir octanoate group than in the oseltamivir phosphate group, these were not serious and the incidence was not significantly different from that in adults treated with laninamivir octanoate, suggesting that there is no particular safety problem. Also, none of the adverse events that occurred more frequently in children than in adults (pyrexia, bronchitis, gastroenteritis, delirium, abnormal behaviour, epistaxis, upper respiratory tract inflammation) were serious, suggesting that these events do not pose a safety problem for now. Taking account of these observations, the submitted clinical study results were assumed to indicate no safety problem in single dose inhalation of laninamivir octanoate 20 mg or 40 mg in pediatric patients with influenza virus infection.

Oseltamivir phosphate, a similar drug to laninamivir octanoate, is reported to be associated with psychiatric disorders/neurologic symptoms, such as abnormal behaviour in patients with influenza virus infection. Since adverse events of delirium and abnormal behaviour were observed in the laninamivir octanoate group as well, the risk of psychiatric disorders/neurologic symptoms in the use of laninamivir octanoate is reviewed in detail in the following section "4.(ii).B.(2).2) Occurrence of psychiatric disorders/neurologic symptoms after the administration of laninamivir octanoate in children."

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

4.(ii).B.(2).2) Occurrence of psychiatric disorders/neurologic symptoms after the administration of laninamivir octanoate in children

PMDA asked the applicant to explain the risk of psychiatric disorders/neurologic symptoms including abnormal behaviour associated with the administration of laninamivir octanoate in children with influenza virus infection based on the safety data obtained from studies in children.

The applicant responded as follows:
The following table shows adverse events that occurred in studies in children that were classified into psychiatric disorders/neurologic symptoms such as abnormal behaviour. The incidence was 3.3% (9 of 276 patients) in the entire population, the breakdown of which includes 5.0% (6 of 120 patients) in the study in patients aged 10 to 19 years (Study CS8958-A-J303) and 2.5% (3 of 123 patients) in the study in patients aged ≤9 years (Study CS8958-A-J302). The events were all mild and resolved. The incidence of the events by dose was 3.0% (4 of 134 patients) in the laninamivir octanoate 20 mg group and was 3.8% (5 of 131 patients) in the laninamivir octanoate 40 mg group, showing no trend toward dose-dependent increase.

According to the "Results of Studies of the Oseltamivir Phosphate Clinical Working Group (June 16, 2009)" published by the Clinical Working Group of Subcommittee on Drug Safety, Committee on Drug Safety, the Pharmaceutical Affairs and Food Sanitation Council, Ministry of Health, Labour, and Welfare, abnormal behaviour was observed in 11% (840 of 7438 patients) of patients who were treated with oseltamivir phosphate, in 13% (286 of 2228 patients) of those who were not, and in 12% (1126 of 9666 patients) of the entire population surveyed. As compared with the results of these studies, psychiatric disorders/neurologic symptoms such as abnormal

behaviour/speech observed in the studies of laninamivir octanoate in children did not show any trend toward increased incidence.

Subjects who showed influenza-associated abnormal behaviour and psychiatric disorders/neurologic symptoms

Subject ID code	Event in preferred term [a] (Term entered in CRF)	Laninamivir octanoate dose (mg)	Age (yrs)	Sex	Virus type/subtype	Most recent body temperature (°C) [b]	Time to onset [c]	Causal relationship
001*	Delirium (Talking in delirium)	20	[redacted]	F	A/H3N1	39.8	32:40	Not related
002*	Crying (Starting crying)	20	[redacted]	F	A/H1N1	41.1	20:00	Related
003*	Abnormal behaviour (Abnormal behaviour)	40	[redacted]	F	A/H1N1	39.3	25:00	Not related
004*	Delirium (Talking in delirium)	20	1[redacted]	M	A/H3N2	39.7	11:30	Not related
005*	Abnormal behaviour (Abnormal behaviour)	20	1[redacted]	M	A/H3N2	39.2	19:15	Not related
006*	Abnormal behaviour (Meaningless action)	40	1[redacted]	M	A/H1N1	38.0	22:00	Related
007*	Fear (Fear)	40	1[redacted]	M	A/H1N1	38.6	34:00	Not related
008*	Verbigeration (Threadless talk)	40	1[redacted]	F	A/H3N2	37.2	52:00	Related
009*	Delirium (Talking in delirium)	40	1[redacted]	F	B	38.4	10:30	Related

a) MedDRA/J V.12.0
b) Body temperature measured at the nearest time point to the first observation of abnormal behaviour/speech
c) "Date and time of the onset of abnormal behaviour/speech" – "date and time of the onset of influenza"

Based on these results and literature-based discussion, the applicant considers that patients treated with laninamivir octanoate did not show a trend toward increased incidence of psychiatric disorders/neurologic symptoms such as abnormal behaviour/speech. However, the accumulated safety data are not robust enough to completely rule out the possibility of psychiatric disorders/neurologic symptoms such as abnormal behaviour caused by laninamivir octanoate. Therefore, precautionary statements on abnormal behaviour and other psychiatric disorders/neurologic symptoms should be included in the "Precautions" section of the package insert in line with the safety measures taken the similar drugs, and safety information should be further collected and analyzed after the market launch.

PMDA generally accepted the applicant's explanation. However, since the available safety information of laninamivir octanoate in children is limited, similar precautions should also be provided for the use in children, and data on the occurrences of psychiatric disorders/neurologic symptoms such as abnormal behaviour should further collected after the market launch to provide information to healthcare professionals as needed.

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

4.(ii).B.(2).3) Safety in high-risk patients

Of patients with a high-risk factor affecting the severity and recovery of influenza virus infection, safety of laninamivir octanoate in (a) infants, (b) the elderly, (c) patients with renal impairment, (d) pregnant and lactating women, (e) patients who have respiratory complications, and (f) patients who have chronic heart disease is described below.

(a) Safety in infants

The applicant explained the safety of laninamivir octanoate in infants aged ≤5 years as follows:
In infants aged ≤5 years with influenza virus infection, the incidence of adverse events was 35.7% (10 of 28 patients) in the laninamivir octanoate group and was 50.0% (8 of 16 patients) in the oseltamivir phosphate group. Adverse events observed in the laninamivir octanoate group were diarrhoea and gastroenteritis in 2 patients (7.1%, 2 of 28 patients) each, vomiting, otitis media, otitis media acute, paronychia, AST increased, ALT increased, gamma-glutamyl transferase (γ-GTP) increased, delirium, epistaxis, and upper respiratory tract inflammation in 1 patient (3.6%, 1 of 28 patients) each. As compared with the incidence of adverse events observed in the entire pediatric patients treated with laninamivir octanoate (27.9%, 77 of 276 patients), the incidence in infants was slightly higher. Of these, 1 patient who showed AST increased, ALT increased, and γ-GTP increased was found to have been treated with both laninamivir octanoate 20 mg and oseltamivir phosphate 44 mg by mistake. Adverse events observed in the oseltamivir phosphate group were bronchitis and upper respiratory tract inflammation in 2 patients (12.5%, 2 of 16 patients) each, and stomatitis, vomiting, gastroenteritis, parotitis, rhinitis, sinusitis, tonsillitis, and cough in 1 patient (6.3%, 1 of 16 patients) each.

PMDA considers that although currently available data do not suggest any particular problems in the safety of laninamivir octanoate in infants, taking account of the limited number of patients treated and of the discussion on the risk of psychiatric disorders/neurologic symptoms [see "4.(ii).B.(2).2) Occurrence of psychiatric disorders/neurologic symptoms after administration of laninamivir octanoate in children"], the collection of safety information of laninamivir octanoate in infants should be further collected after the market launch.

(b) Safety in the elderly

The incidence of adverse events in patients aged ≥65 years with influenza virus infection was 27.8% (5 of 18 patients) in the laninamivir octanoate group and was 12.5% (1 of 8 patients) in the oseltamivir phosphate group. Adverse events observed in the laninamivir octanoate group were diarrhoea in 2 patients (11.1%, 2 of 18 patients), tachycardia, bronchopneumonia, oral herpes, platelet count increased, decreased appetite, and dizziness in 1 patient (5.6%, 1 of 18 patients) each. The adverse event observed in the oseltamivir phosphate group was epistaxis in 1 patient (12.5%, 1 of 8 patients). The laninamivir octanoate 20 mg single dose inhalation group included 8 patients aged ≥65 years and had advese events observed in 2 patients (25.0%), while the laninamivir octanoate 40 mg single dose inhalation group included 10 patients aged ≥65 years and had advese events observed in 3 patients (30.0%). Based on these results, the applicant explained that, in patients aged ≥65 years with influenza virus infection who were treated with laninamivir octanoate, there was no trend toward an increase in specific adverse events or in the incidence of overall adverse events in association with the use of laninamivir octanoate.

PMDA considers that although the available data do not suggest any particular problems in the safety of laninamivir octanoate in the elderly at the current moment, taking account of the limited number of elderly patients treated with laninamivir octanoate in clinical studies precluding the safety evaluation in the elderly for now, data should be further collected after the market launch.

(c) Safety in patients with renal impairment

PMDA asked the applicant to explain the safety of laninamivir octanoate in patients with renal impairment.

The applicant responded as follows:
In clinical studies of laninamivir octanoate in patients with influenza virus infection, "patients who have renal impairment" is an exclusion criterion and therefore laninamivir octanoate was not administered to patients who had renal impairment. For this reason, the safety of laninamivir octanoate in patients with influenza virus infection who have renal impairment has not been

established. In the PK study in subjects with decreased renal function (Study CS8958-A-J105) in which laninamivir octanoate 20 mg was administered by inhalation in a single dose to uninfected subjects with normal or decreased renal function, adverse events as shown in the following table were observed. ALT increased and AST increased were observed only in the severely decreased renal function group. These adverse events occurred in one patient during a test performed at 48 hours after administration. The events were considered mild in the degrees of increases and resolved without any intervention. Therefore, laninamivir octanoate was considered not to pose any significant safety problem in patients with severely decreased renal function.

Occurrence of adverse events in PK study in patients with decreased renal function

System Organ Class (SOC)	Preferred term (PT) [a)]	Normal function group (N = 7)	Mild impairment group (N = 4)	Moderate impairment group (N = 5)	Severe impairment group (N = 4)
		No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)	No. of patients with event (%)
Gastrointestinal disorders	Diarrhoea	2 (28.6)	0 (0.0)	1 (20.0)	1 (25.0)
General disorders and administration site conditions	Hunger	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
Investigations	ALT increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
	AST increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
	Blood potassium increased	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)
	Blood urea increased	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
	Urobilin urine present	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	Back pain	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
	Neck pain	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)

a) Adverse event terms entered in the case report form (CRF) were replaced by preferred terms of MedDRA/J Ver. 11.0.

PMDA considers as follows:
There is a lack of information on the safety of laninamivir octanoate administered to patients with influenza virus infection who have renal impairment because only patients without influenza virus infection were eligible for the clinical studies. Therefore, relevant data should be further collected after the market launch to investigate the safety of laninamivir octanoate in patients with influenza virus infection who have renal impairment. The dose and administration in patients with renal impairment is discussed in "4.(ii).B.(3).3) Dosage and administration in patients with renal impairment."

(d) Safety in pregnant women and fetuses

The applicant explained the safety of laninamivir octanoate in patients who had influenza virus infection during pregnancy or lactation, as follows:
The study protocols excluded "pregnant patients or patients who may be pregnant, lactating patients, and patients who wish to become pregnant during the study period" and therefore the safety of laninamivir octanoate in pregnant or lactating women was not investigated. However, in the global phase III study (Study CS8958-A-J301), 1 patient received the study drug before her pregnancy test result was carefully checked. Later, the patient was found to have been in approximately 15 weeks of pregnancy at the time of the administration of the study drug. In this patient, fetal cerebral ventricle dilatation as well as postnatal brain malformation, low set ears, and micrognathia were observed. These congenital malformations were reported as serious adverse events. The mother (subject) took laninamivir octanoate around 15 weeks of pregnancy,

the latter stage of relatively sensitive period. This phase is close to the next phase of 16 to 19 weeks of pregnancy, the less sensitive period during which congenital anomaly generally does not occur. Thus, it is considered the patient received the drug when congenital anomaly was unlikely to occur or, even if had occurred, would be found at only limited sites such as the palate and external genitalia.

The investigator considered that the adverse events were related to the study drug because a relationship between the events and the study drug could not be completely ruled out, while noting that (a) influenza virus infection during the fetal period per se may be a risk factor, and (b) the possibility that congenital anomaly or fetal cerebral ventricle dilatation might have contributed to the postnatal abnormalities still remain.

PMDA considers as follows:
Given the mechanism of action of laninamivir octanoate against influenza virus infection, it is understandable that laninamivir octanoate should be administered as soon as possible. However, the above-described patient was treated with laninamivir octanoate before her pregnancy test result became available, for the reason that the patient had denied the possibility of her pregnancy during an interview. This was a careless action of concern in terms of the safety for the patient. Considering (a) that the reproductive and developmental toxicity studies of laninamivir octanoate revealed no toxicological effects in offspring that were caused by the administration of laninamivir octanoate to their parental animals [see "3.(iii).A.(5) Reproductive and developmental toxicity"], which suggests that the risk of laninamivir octanoate-induced teratogenicity is not necessarily high, and (b) that the organogenesis phase of the central nervous system, where the malformations primarily occurred, was inconsistent with the timing of the administration of laninamivir octanoate (around 15 weeks of pregnancy), a causal relationship of the serious adverse event with multiple malformations in the newborn and laninamivir octanoate is unclear, and thus the event could have been incidental. Taking account of all available information, the aforementioned case does not necessarily warrant the entire restriction of the administration of laninamivir octanoate to pregnant women. Nevertheless, a possible effect of laninamivir octanoate on congenital anomaly cannot be excluded completely, and therefore, it should be cautioned that the use of laninamivir octanoate is not allowed in pregnant women or women who may possibly be pregnant unless the expected therapeutic benefit outweighs the possible risk associated with treatment as are the cases with similar drugs, because there is only limited information so far available on the safety of laninamivir octanoate during pregnancy on mothers and their children. Information on the safety of laninamivir octanoate in pregnant women should be collected after the market launch, and obtained information should be promptly provided to clinical practices.

(e) Safety in patients who have respiratory complications
PMDA asked the applicant to explain the safety of laninamivir octanoate in patients who have underlying chronic respiratory disease (e.g., bronchial asthma, chronic obstructive pulmonary disease [COPD]).

The applicant responded as follows:
In clinical studies of laninamivir octanoate, to ensure the accuracy of evaluation of efficacy and safety, patients who had chronic respiratory disease such as bronchial asthma and COPD were excluded in accordance with the exclusion criteria. The safety of laninamivir octanoate in this population was therefore not evaluated. Among adverse events suggestive of asthma observed in clinical studies, wheezing and asthma (reported event name, asthmatic bronchitis) were observed in 1 infected pediatric patient each, both in the laninamivir octanoate group. The patient who developed wheezing was a 13-year-old boy. He had a history of bronchial asthma but had no complications. Wheezing occurred 1 day after the administration of laninamivir octanoate but resolved on the day of the onset after treatment with a bronchodilator, etc. The patient who

developed asthma (asthmatic bronchitis) was a 9-year-old girl who had a history of febrile convulsions and had concurrent allergic rhinitis. Asthma occurred 15 days after the administration of laninamivir octanoate but resolved 18 days after the onset by treatment with drugs including a bronchodilator. The causal relationship of each adverse event with laninamivir octanoate inhalation was ruled out by the investigator.

A randomized, double-blind, comparative study with oseltamivir phosphate (CS8958-A-J305 study) is ongoing in patients with influenza virus infection who have chronic respiratory disease. [redacted]. Under blinded conditions, adverse events were reported by 16 patients ([redacted]%), including aggravated asthma in 4 patients and cough in 1 patient. A causal relationship with laninamivir octanoate inhalation was ruled out for all these events.

Thus, adverse drug reactions such as bronchospasm and dyspnoea, which were observed with similar inhalation drugs, have not been observed in clinical studies of laninamivir octanoate. The applicant therefore considers that there are no inhalation-associated safety problems for now. However, safety information will be further collected from the ongoing clinical study and the post-marketing surveillance, etc. Also, caution for use of laninamivir octanoate in patients with chronic respiratory disease will be provided in the "Important Precautions" section of the package insert, and information on serious adverse drug reactions observed with similar drugs will be provided in the "Adverse Reactions" section.

PMDA considers that there is scant information on the safety of laninamivir octanoate in patients who have underlying chronic respiratory disease (e.g., bronchoasthma, COPD), and it should be advised that the safety of laninamivir octanoate in patients who have underlying chronic respiratory disease (e.g., bronchoasthma, COPD) is not established at the current moment and, at the same time, to collect information on the safety of laninamivir octanoate in these patients after the market launch.

(f) Safety in patients who have chronic heart disease

The applicant explained the safety of laninamivir octanoate in patients with chronic heart disease as follows:

Among adult patients with influenza infection, 12 patients in the laninamivir octanoate group and 4 patients in the oseltamivir phosphate group had chronic heart disease. Of these, 33.3% (4 of 12 patients) in the laninamivir octanoate group and 50.0% (2 of 4 patients) in the oseltamivir phosphate group had adverse events. Adverse events observed in the laninamivir octanoate group were diarrhoea in 2 patients (16.7%, 2 of 12 patients), thrombocytopenia, palpitations, white blood cell count decreased, eosinophil percentage increased, neutrophil percentage decreased, monocyte percentage increased, lymphocyte percentage increased, and migraine in 1 patient each (8.3%, 1 of 12 patients). Adverse events observed in the oseltamivir phosphate group were abdominal pain upper, cheilitis, white blood cell count decreased, neutrophil percentage decreased, lymphocyte percentage increased, and cough in 1 patient each (25.0%, 1 of 4 patients). These results showed that there was no marked increase in the incidence of adverse events, or increase in any specific adverse events, in patients with chronic heart disease as compared with the entire population treated with laninamivir octanoate.

Although no patients with chronic heart disease experienced adverse events that were considered attributable to their underlying chronic heart disease, the number of these patients enrolled in the clinical studies of laninamivir octanoate were as small as 12. PMDA therefore considers safety data of laninamivir octanoate in patients with chronic heart disease should be further collected after the market launch.

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

The applicant considers that there was no risk of QT/QTc interval prolongation that could pose a problem in the clinical use of laninamivir octanoate based on the results of nonclinical safety pharmacology studies [see "3.(i).A.(3) Safety pharmacology"]. PMDA asked the applicant to summarize QT/QTc prolongation-related safety information of laninamivir octanoate and its active metabolite R-125489 and explain the risk of prolonged QT/QTc interval that could be induced by laninamivir octanoate.

The applicant responded as follows:

In the clinical pharmacology study in non-infected subjects in Japan, there were no adverse events that were classified into the system organ class (SOC) of cardiac disorders. In clinical studies in patients with influenza infection (1295 patients in safety analysis set), palpitations (2 patients), tachycardia (1 patient), and ventricular extrasystoles (1 patient) occurred, which were all mild in severity. In the clinical studies in patients with influenza virus infection, electrocardiography (ECG) was not performed.

The analysis of 12-lead ECG recorded in the clinical pharmacology study in non-infected subjects in Japan showed that there were no patients who showed the absolute value of QTcB (Bazett's correction formula) or QTcF (Fridericia's correction formula) exceeding 450 msec up to 24 hours after administration on Day 3 in multiple inhalations of laninamivir octanoate 20 or 40 mg BID for 3 days (5 doses in total), or until 24 hours after single dose inhalation of laninamivir octanoate 80 or 120 mg. There were no patients in whom the change in QTcB from the day before administration (ΔQTcB) exceeded 30 msec. On the other hand, the change in QTcF from the day before administration (ΔQTcF) exceeded 30 msec in 1 of 8 patients after single dose inhalation of laninamivir octanoate 80 mg, in 2 of 8 patients after a single dose inhalation of 120 mg, and in 1 of 6 patients after 20 mg multiple dose inhalation. Low QTcF was observed on the day before administration in all these patients, and similar changes were observed in 2 of 4 patients in the placebo group in the study with single dose inhalation of 80 or 120 mg. A comparison of QTc intervals (QTcF, ΔQTcF) at 4 hours after administration with those in the placebo group and an investigation of the relationship between plasma concentrations (of laninamivir octanoate, active metabolite R-125489) and QTc intervals did not show a trend toward prolonged QTc interval caused by laninamivir octanoate.

Based on these findings, the applicant considers that there is no particular concern about the safety of laninamivir octanoate relating to prolonged QT/QTc interval, when laninamivir octanoate is used according to the proposed dosage and administration.

PMDA concluded as follows:

In the clinical studies of laninamivir octanoate, no statistically significant difference was observed between the laninamivir octanoate group and the placebo group in QTc intervals on the day before administration and at 4 hours after administration. Also, there was no clear trend toward dose-dependent prolongation of QTc intervals. Therefore, PMDA accepts the applicant's explanation that there is no particular concern about the safety of laninamivir octanoate related to QT/QTc interval prolongation, when laninamivir octanoate is used according to the proposed dosage and administration.

4.(ii).B.(3) Dosage and administration

4.(ii).B.(3).1) Dosage and administration of laninamivir octanoate

The applicant proposed the following dosage and administration for laninamivir octanoate: "The usual dose for adults and children is 40 mg of laninamivir octanoate administered by inhalation in a single dose," and explained as follows:

In order to determine the most appropriate recommended clinical dosage and administration in adults, efficacy was compared between single dose inhalation of laninamivir octanoate 20 mg or

40 mg in the global phase III study (Study CS8958-A-J301) and inhalation of laninamivir octanoate 20 mg QD for 2 days in the Japanese phase II multiple dose study (Study CS8958-A-J203). As a result, a 40 mg single-dose was not only effective in the entire population but also demonstrated generally consistent efficacy against different viral types or subtypes as well as in other subgroups, based on which the recommended dose of laninamivir octanoate in adult patients was considered to be 40 mg. Taking account of the results of the phase II multiple dose study (Study CS8958-A-J203) in Japan, inhaled laninamivir octanoate 20 mg QD for 2 days and of a single dose of laninamivir 40 mg were both considered effective. However, multiple-dose treatment is more likely to fail to complete, and therefore single-dose administration is ideal to ensure compliance when the efficacy of the 2 regimens is comparable. Based on these findings, the applicant determined that single dose inhalation of 40 mg was the most appropriate recommended clinical dosage and administration for laninamivir octanoate in adult patients.

In children, the efficacy of single dose inhalation of laninamivir octanoate 20 mg or 40 mg was compared between the results of the study in patients aged ≤9 years (Study CS8958-A-J302) and the study in patients aged 10 to 19 years (Study CS8958-A-J303) and the global phase III study (Study CS8958-A-J301) conducted in adults, and the recommended clinical dosage and administration was determined based on the similarity or difference in the efficacy between children and adults. In the study in patients aged ≤9 years (Study CS8958-A-J302), the difference (95% CI) in the median time to alleviation of symptoms between the laninamivir octanoate groups and the oseltamivir phosphate group was −31.0 (−50.3 to −5.5) hours in the laninamivir octanoate 20 mg group and was −31.9 (−43.4 to 0.5) hours in the laninamivir octanoate 40 mg group, demonstrating early improvement of ≥30 hours in the laninamivir octanoate groups as compared with the oseltamivir phosphate group, which suggested single dose inhalation of laninamivir octanoate 20 mg and 40 mg were both effective. Since the study in patients aged 10 to 19 years (Study CS8958-A-J303) was an uncontrolled study, efficacy cannot be evaluated from the result of this study alone. However, the median times to alleviation of symptoms in the laninamivir octanoate 20 and 40 mg single dose inhalation groups were similar to that observed in the global phase III study (Study CS8958-A-J301), which suggested that these dosages were similarly effective in patients aged 10 to 19 years with influenza virus infection as in adults.

Underdosing of an antiviral drug generally increases a risk of drug resistance. It is also reported that children are prone to resistance acquisition as compared with adults.[60] Therefore, children should receive as high dose of the drug as possible with acceptable safety. The applicant then concluded that single dose inhalation of 40 mg should be the best as recommended clinical dosage and administration of laninamivir octanoate in pediatric patients, as with adults.

Based on these findings, the proposed dosage and administration is "the usual dosage for adults and children is 40 mg of laninamivir octanoate administered by inhalation in a single dose."

Considering that time to alleviation of symptoms and time for body temperature to return to normal were similar between the laninamivir octanoate 20 mg and 40 mg groups in the study in patients aged ≤9 years, PMDA asked the applicant to explain the reason why the recommended clinical dose of laninamivir octanoate in children aged ≤9 years was defined not as 20 mg but as 40 mg, based on the efficacy and safety data in the study in this age group.

The applicant responded as follows:
The percentage of subjects with a viral titer of below the detection limit (1.5 $\log TCID_{50}$/mL) on Day 3 (Visit 2) was higher in the laninamivir octanoate 40 mg group than in the 20 mg group and the adjusted mean of viral titer (mean viral titer adjusted for the titer at Visit 1) on Day 3 (Visit 2) was lower in the laninamivir octanoate 40 mg group than in the 20 mg group. In the both groups,

[60] *Lancet*. 2004;364(9436):759-65

virus eradication was confirmed on Day 3 in approximately half of the subjects, but the percentage was higher in the laninamivir octanoate 40 mg group (57.4%) than in the laninamivir octanoate 20 mg group (48.3%), and the adjusted mean of the titer ($logTCID_{50}$/mL) was lower in the laninamivir octanoate 40 mg group (1.88) than in the laninamivir octanoate 20 mg group (2.10). Since laninamivir octanoate exhibits its antiviral effect based on NA inhibitory activity, earlier eradication of the virus is important from the viewpoint of efficacy and is also necessary for the prevention of drug resistance.

The median time to alleviation of symptoms of influenza B virus infection tended to be slightly shorter in the laninamivir octanoate 40 mg group than in the laninamivir octanoate 20 mg group. According to the statistics in the 2006/07 season (the season of mixed epidemic with type A and B), influenza B virus affected mostly children aged ≤19 years, with the majority of those aged 7 to 13 years.[61] Generally, influenza B virus mutates more slowly than influenza A virus. As was the case with the 2006/07 season, influenza B virus does not become epidemic in adults in some seasons, while the virus becomes epidemic in almost every season in children because their immunity is still relatively immature. Therefore, efficacy against influenza B virus is also important in pediatric patients.

In the study in patients aged ≤9 years (Study CS8958-A-J302), the incidence of adverse events was 29.3% (36 of 123 patients) in the laninamivir octanoate groups combined, 34.4% (21 of 61 patients) in the 20 mg group, and 24.2% (15 of 62 patients) in the 40 mg group, showing no trend toward dose-dependent increase. Common adverse events in the both groups were also similar, which included diarrhoea (6.6% [4 of 61 patients] in the laninamivir octanoate 20 mg group, 3.2% [2 of 62 patients] in the laninamivir octanoate 40 mg group), vomiting (4.9% [3 of 61 patients], 3.2% [2 of 62 patients]), bronchitis (4.9% [3 of 61 patients], 1.6% [1 of 62 patients]), gastroenteritis (6.6% [4 of 61 patients], 1.6% [1 of 62 patients]), nasopharyngitis (1.6% [1 of 61 patients], 3.2% [2 of 62 patients]), and upper respiratory tract inflammation (4.9% [3 of 61 patients], 6.5% [4 of 62 patients]). Rash (0.0% [0 of 61 patients], 3.2% [2 of 62 patients]) was observed only in the laninamivir octanoate 40 mg group, but its causal relationship with the study drug was ruled out and the both of 2 patients recovered in both patients after the administration of therapeutic agents. The event was therefore considered to pose no significant safety problem.

Based on these findings, the applicant considers that laninamivir octanoate 40 mg is more appropriate than 20 mg from the viewpoint of both efficacy and safety.

PMDA considers as follows:
A relationship between dose and a risk of induction of drug-resistant virus remains unclear, although the applicant considers it a basis for selecting single dose inhalation of laninamivir octanoate 40 mg as the appropriate recommended dose rather than 20 mg. However, the rest of the applicant's explanation is acceptable, and therefore it is appropriate to define the dosage and administration of laninamivir octanoate as 40 mg single dose inhalation for non-high-risk patients with influenza virus infection both in adults and children.

This conclusion of PMDA is going to be discussed at the Expert Discussion.

4.(ii).B.(3).2) Equivalence between the inhaler used in clinical studies and one for commercial use

[redacted]

[61] Infectious Agents Surveillance Report (IASR) of Infectious Disease Surveillance Center, National Institute of Infectious Diseases: Influenza in the 2006/2007 season: IASR. 2007 Nov;28(11):311-3 available from: http://idsc.nih.go.jp/iasr/28/333/tpc333-j.html

[redacted].

The applicant explained the equivalence between the inhaler for clinical studies and the one for commercial use as follows:
The equivalence in inhalation characteristics between TwinCaps and Inhaler A was confirmed *in vitro* prior to the manufacturing of the commercial formulation [see "4.(i).A.(1) Evaluation of the equivalence of *in vitro* inhalation characteristics"]. In addition, the study to compare inhalers (Study CS8958-A-304) was conducted to evaluate the efficacy of laninamivir octanoate with use of the different inhalers [see "4.(ii).A.(3).4) Phase III study in adult patients with influenza virus infection to compare inhaling devices"].

In the study to compare inhalers (Study CS8958-A-304), the primary efficacy endpoint of the median times to alleviation of symptoms were similar between the TwinCaps group (72.0 hours) and the Inhaler A group (78.0 hours) with the difference (95% CI) in the median time of −6.0 (−23.9 to 6.7) hours. The TwinCaps group was not inferior to the Inhaler A group in any other parameters including the secondary endpoints. The incidence of adverse events was not significantly different between the 2 inhaler groups, showing no safety problems in either group. Based on these results, the applicant considered that there is no significant difference between the 2 inhalers and therefore there were no problems with submitting the application for the commercial product with TwinCaps.

PMDA considers as follows:
The drug delivery efficiency to the lungs and the resulting efficacy by inhaler are difficult to estimate *in vitro*, and these need to be evaluated based on clinical efficacy following actual administration to patients. For laninamivir octanoate, the study to compare inhalers (Study CS8958-A-304) was conducted before the replacement of Inhaler A by TwinCaps. As a result, the primary endpoint of time to alleviation of symptoms was similar, and TwinCaps was not inferior to Inhaler A in any other parameters including secondary endpoints. Also, the incidences of adverse events were not significantly different between the 2 inhalers, showing similar safety profiles. Therefore, there is no major problem in the use of TwinCaps as inhaler for the commercial drug product.

4.(ii).B.(3).3) Dosage and administration in patients with renal impairment
PMDA considers the dosage and administration in patients with renal impairment as follows:
In clinical studies of laninamivir octanoate in patients with influenza virus infection, "patients who have renal impairment" was an exclusion criterion and therefore no safety information is available for these patients. Instead, a clinical study was conducted in patients without influenza virus infection who have renal impairment, from which C_{max} and $AUC_{0\text{-}inf}$ of the active metabolite of laninamivir octanoate, R-125489, were reported to have increased by approximately 1.9 fold and 5 fold, respectively, in patients with severely decreased renal function (CL_{CR} <30 mL/min). In the clinical study with a single dose inhalation of laninamivir octanoate to healthy subjects, no significant safety problem was observed at doses of up to 120 mg. Another study with multiple inhalations of the drug up to a total dosage of 200 mg (40 mg twice daily for a total of 5 doses) also found no significant safety problem. On the other hand, a relationship between renal function and the safety of laninamivir octanoate was evaluated and was stratified by eGFR in the clinical studies of laninamivir octanoate in patients with influenza virus infection, namely the phase II single dose study (Study CS8958-A-J201) in Japan, the phase II study (Study CS8958-A-A202) in Taiwan, the phase II multiple dose study (Study CS8958-A-J203) in Japan, the global phase III study (Study CS8958-A-J301), and the study to compare inhalers (Study CS8958-A-J304) [see "4.(i).B.(2) Dosage and administration in patients with decreased renal function"]. Although the incidence of adverse events was slightly higher in patients with low eGFR than in patients with normal renal function, a dose-dependent change was not clearly seen in the incidence of adverse

events with laninamivir octanoate, and this suggests no significant safety problem.

Based on these findings, PMDA considers that dose adjustment of laninamivir octanoate is not necessary for patients who have renal impairment, and there is no harm in treating these patients with a 40 mg single-dose, the same dosage regimen as for patients with normal renal function. However, due to limited experience in the administration of laninamivir octanoate to patients with renal impairment and no experience in those with severely decreased renal function, safety information of patients with renal impairment who are treated with laninamivir octanoate should be collected after the market launch.

This conclusion of PMDA is going to be discussed at the Expert Discussion.

4.(ii).B.(4) Indication

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

However, the evaluation of efficacy of laninamivir octanoate by virus type, a secondary efficacy endpoint [see "4.(ii).B.(1).3).(a) Efficacy by type of influenza virus"], revealed lack of robust evidence that supports the efficacy of laninamivir octanoate against A/H3N2 subtype in children. In adults with A/H3N2 subtype, time to alleviation of symptoms was shorter in the laninamivir octanoate 40 mg group than in the laninamivir octanoate 20 mg group, showing a dose-dependent relationship, whereas no decreasing trend in time to alleviation of symptoms nor dose dependent-relationship was seen in children with A/H3N2 subtype. Therefore, information on the efficacy of the drug product by influenza virus type/subtype including the efficacy in children with A/H3N2 should be further collected after the market launch.

This conclusion of PMDA is going to be discussed at the Expert Discussion.

4.(ii).B.(5) Clinical positioning

4.(ii).B.(5).1) Clinical positioning of laninamivir octanoate

The applicant explained the clinical positioning of laninamivir octanoate as follows. (a) laninamivir octanoate is equally effective as oseltamivir phosphate and does not have particular safety problems, (b) in clinical situations where the completion of a course of treatment is essential for children due to their prolonged virus release, laninamivir octanoate is useful as it requires only a single dose to complete treatment, (c) laninamivir octanoate is less likely to generate drug-resistant viruses, and (d) laninamivir octanoate can be used in patients with different characteristics.

In adult patients, laninamivir octanoate 40 mg demonstrated efficacy against influenza virus infection which is comparable to that of oseltamivir phosphate (BID 5-day oral administration). Laninamivir octanoate was also as effective in adolescent patients aged 10 to 19 years as in adult patients. In pediatric patients aged ≤9 years, laninamivir octanoate decreased time to alleviation of symptoms by approximately 30 hours as compared with oseltamivir phosphate. The safety analysis revealed that common adverse events after the administration of laninamivir octanoate were gastrointestinal disorders such as diarrhoea both in adults and in children, the frequencies of which were comparable with those observed with oseltamivir phosphate. There was no trend toward a dose-dependent increase in specific adverse events or adverse drug reactions, and favorable safety profile was shown. Based on these findings, a single dose inhalation of laninamivir octanoate at 40 mg is considered safe and sufficiently effective for the treatment of influenza virus infection, in contrast to existing NA inhibitors oseltamivir phosphate and zanamivir hydrate, both of which require to be administered twice daily for 5 days.

Generally, children are extremely prone to influenza virus infection as compared with adults, and an outbreak and spread of infection take place during their group activities such as in schools. A contributory factor of this is thought to be the virus persistently released from a patient with improving symptoms. Incomplete treatment for infection may pose a risk of further spread of infection. The completion of treatment is therefore essential to avoid such situations, and laninamivir octanoate is considered to have characteristics suitable to the treatment of influenza virus infection.

In the 2008/09 season, almost all A/H1N1 subtypes were oseltamivir phosphate-resistant, against which laninamivir octanoate was shown to have anti-viral activity and clinical efficacy. *In vitro* studies showed that laninamivir octanoate generally has NA-inhibitory activity against known oseltamivir-resistant virus strains and has favorable NA-inhibitory activity against type B viruses known to be zanamivir hydrate-resistant. Therefore, laninamivir octanoate is less likely to develop cross-resistance to existing drugs and is expected to be effective against not only seasonal influenza viruses but also viruses resistant to existing drugs that may emerge in future. The drug product is thus considered a useful novel treatment option.

In the elderly, pregnant women, infants and toddlers, and patients who have an underlying disease (chronic respiratory illness, chronic heart disease, metabolic disease, renal impairment, immune dysfunction), it is known that aggravation of the underlying disease, secondary bacterial infection, etc. may increase a risk of hospitalization or death, and therefore they are recognized as high-risk patients. In high-risk patients, vaccination should be ensured as the basics of prevention and, should influenza virus infection be noticed, early treatment with an antiviral drug is critical. Many reports on disease aggravation or death in high-risk patients resulting from a spread of pandemic influenza virus also indicate the importance of treatment in this population and therefore laninamivir octanoate is expected to be used in this population.

In clinical studies of laninamivir octanoate in adults, patients with chronic respiratory illness, patients with chronic renal impairment, and pregnant women were excluded and, in clinical studies in children, patients with chronic respiratory illness, chronic heart disease, metabolic disease, renal impairment, and immune dysfunction were excluded. The efficacy of laninamivir octanoate was therefore not evaluated in these patients. The number of high-risk patients who were eligible for the clinical studies was too small for efficacy evaluation. In the elderly patients ($\geq$ 65 years of age), no consistent effect was seen on either time to alleviation of symptoms or time for body temperature to return to normal. The efficacy in young children (3-5 years of age) and patients who have metabolic disease (primarily diabetes mellitus) or chronic heart disease was not evaluated individually. In the safety analyses, there were no findings suggestive of conditions such as aggravation of the underlying disease and progression of influenza virus infection that are likely in high-risk patients. Oseltamivir phosphate is reported to decrease risks in high-risk patients such as the development of pneumonia, the use of antibacterial agents, and hospitalization associated with influenza virus infection. Similarly, laninamivir octanoate is expected to be effective in these high-risk patients, if introduced in the early stage of illness. Nevertheless, the drug should be administered while monitoring the patient's condition from the aspect of the prevention of aggravation.

PMDA considers the clinical positioning of laninamivir octanoate in treatment of influenza virus infection as follows:
Laninamivir octanoate is an NA inhibitor and is considered to be effective against both influenza A and B virus, as with similar drugs (oseltamivir phosphate, zanamivir hydrate, peramivir hydrate). Since treatment with laninamivir octanoate is completed with a single-dose inhalation, it is expected to be more convenient and improve patient compliance with the treatment, so it will further ensure the completion of treatment. Therefore, laninamivir octanoate is an antiviral drug against influenza useful for patients with potentially poor compliance.

Given the status of the outbreaks of resistant viruses in recent years such as H275Y mutant virus, because of the low risk of the emergence of a drug-resistant virus for now, laninamivir octanoate is valuable as an additional treatment option for influenza. However, the evidence is weak for the applicant's views on the low risk of cross resistance and the efficacy against potentially emerging virus strains resistant to the existing drugs. Therefore, the emergence of virus strains resistant to laninamivir octanoate or other NA inhibitors should be monitored closely even after the market launch.

Laninamivir octanoate is prepared for single-dose inhalation, and it should be used under an appropriate guidance for inhalation. With the clinical positioning of laninamivir octanoate in mind, the preparation of guidelines for the proper use of laninamivir octanoate should be expedited in collaboration with relevant academic societies, etc. so as to be provided to healthcare professionals.

This conclusion of PMDA is going to be discussed at the Expert Discussion.

4.(ii).B.(5).2) Administration of laninamivir octanoate to patients with pandemic influenza virus infection or highly pathogenic avian influenza virus infection

PMDA asked the applicant to explain the clinical efficacy of laninamivir octanoate for the treatment of the pandemic influenza A/H1N1 virus infection or highly pathogenic avian influenza A/H5N1 virus infection.

The applicant responded as follows:
The active metabolite of laninamivir octanoate R-125489, similarly to the standard strains, vaccine strains, and clinical isolates, exhibited a potent inhibitory activity against NA activity of pandemic influenza virus subtype A/H1N1 and highly pathogenic avian influenza virus subtype A/H5N1, and the effect of laninamivir octanoate against both virus strains was also demonstrated in mice infected with these viruses [see "3.(i).A.(1).1) *In vitro* antiviral effect, and 3.(i).A.(1).2) *In vivo* antiviral effect"]. A single intranasal administration of laninamivir octanoate to mice infected with pandemic influenza virus subtype A/H1N1 decreased the viral titer in the lungs, and a single-dose administration of laninamivir octanoate to mice infected with oseltamivir-sensitive or resistant highly pathogenic avian influenza virus subtype A/H5N1 similarly prolonged the survival of the animals. In addition, laninamivir octanoate was shown to prevent the growth of the virus not only in the lungs but also in the brain [see "3.(i).A.(1).4) Study on highly pathogenic avian influenza (H5N1) virus"].

Thus, R-125489 strongly inhibited NA activity regardless of virus type in *in vitro* systems. Also, laninamivir octanoate showed an antiviral effect (viral growth prevention, life-prolonging effect) in *in vivo* animal models of pandemic influenza A/H1N1 virus infection and highly pathogenic avian influenza A/H5N1 virus infection. Taking also account of the clinical efficacy of the drug against seasonal influenza virus infection demonstrated in clinical studies, laninamivir octanoate is expected to be effective in patients with pandemic influenza A/H1N1 virus infection and in those with highly pathogenic avian influenza A/H5N1 virus infection.

At present, no clinical study data are available on the effect of laninamivir octanoate on the both of said viral subtypes. However, in the ongoing (as of [redacted], 20[redacted]) clinical study (Study CS8958-A-J305) in patients with chronic respiratory illness, all currently enrolled subjects are infected with pandemic influenza virus subtype A/H1N1, and efficacy results of laninamivir octanoate in patients with pandemic influenza A/H1N1 virus infection will be available in the future.

PMDA considers as follows:

Based on the nonclinical study data, the applicant expects laninamivir octanoate to be effective against pandemic influenza virus A/H1N1 and against highly pathogenic avian influenza virus A/H5N1, and PMDA considers the applicant's view understandable. However, since there are no clinical study data available at present on the effect of the drug product either against pandemic influenza A/H1N1 virus infection or against highly pathogenic avian influenza A/H5N1 virus infection, the clinical efficacy and the clinical positioning of laninamivir octanoate against infection by these viral subtypes remain unclear. Data should be obtained from the ongoing clinical study in patients with chronic respiratory illness, and information on the clinical efficacy of laninamivir octanoate in patients infected by said virus strains should also be collected after the market launch. New evidence should be provided to clinical practices appropriately once available.

4.(ii).B.(6) Other

4.(ii).B.(6).1) Efficacy in high-risk patients and efficacy of prophylactic administration

The applicant explained the ongoing clinical studies on laninamivir octanoate as follows:
In Japan, the following 2 clinical studies are being conducted: a phase III confirmatory study to obtain the indication for prophylactic administration (Study CS8958-A-J306, prophylactic study) and a study in high-risk patients. The subjects of the study in high-risk patients have chronic respiratory illness (e.g., bronchial asthma, COPD) as underlying disease and, according to the counting as of [redacted], 20[redacted], ≥90% of enrolled subjects had influenza virus infection who have only bronchial asthma as underlying disease. There is no ongoing foreign clinical study at present.

[redacted].

PMDA considers that antiviral drugs against influenza are in high demand for the treatment and prevention of the disease in high-risk patients, who are prone to secondary aggravation, and information on the efficacy and safety of laninamivir octanoate in these patients obtained from the ongoing clinical studies and the post-marketing surveillance should be immediately offered to healthcare professionals once available.

4.(ii).B.(6).2) Measures to ensure correct inhalation

PMDA asked the applicant to explain measures to be taken to ensure dosing compliance and the performance of proper inhalation technique by patients including children, and a current plan on what information and cautions should be provided to healthcare professionals.

The applicant responded as follows:
In efforts to ensure dosing compliance and to enable patients including children to properly inhale the drug product, the applicant intends to design an user-friendly product label and prepare a "guidance for patient education" and "empty sample inhalers (for demonstration)" to be used by healthcare professionals including pharmacists, a "user's manual" to be provided to patients along with the drug product, and "DVDs that instruct how to inhale the drug product (for adults, for children)". The applicant may also provide directions for use on the website. Furthermore, the applicant intends to update the proposed package insert with a precautionary statement to the effect that "laninamivir octanoate should not be administered to the child unless considered capable of inhaling the drug" in the sub-sections of "Pediatric Use" and "Precautions" in the "Precautions" section to ensure that healthcare professionals including pharmacists are able to give proper guidance to patients.

Testers (such as In-Check and Turbutester) are commercially available for the assessment of patients' competence in using dry powder inhalers (DPIs). The devices are designed to measure air flow rates through DPIs such as Diskus, Turbuhaler, and Handihaler, but none of them is

suitable for the inhaler of laninamivir octanoate. Therefore the existing testers will not be not used to determine patients' competence in using laninamivir octanoate.

PMDA generally accepts the applicant's explanation. **S**ince Inavir is an inhaler, healthcare professionals should provide patients with education on inhalation technique. It is even more so because the drug product is formulated for a single dose regimen and patients need to perform the technique without fail. Therefore, to promote the proper use of laninamivir octanoate, difficulties in the performance of the inhalation technique should be further investigated after the market launch, and identified difficulties should be addressed promptly in collaboration with medical institutions, etc.

PMDA considers that eligibility of children for the use of Inavir should not necessarily be restricted by age as with the similar drugs and inhalers, and competence in using the inhaler may be determined on a patient-by-patient basis at the discretion of his or her attending physician. Inavir may be prescribed to the patient when considered competent. For this purpose, the package insert, etc. should contain a description to the effect that "laninamivir octanoate should be administered only to children who are considered competent in the proper use of the drug" along with the relevant information including the age range of children to whom laninamivir octanoate was administered in clinical studies. However, for patients with compromised respiratory function, there are no grounds for decisions on competence in the proper use of the drug product based on the level of compromised respiratory function. Therefore, caution should be used in the administration of laninamivir octanoate to patients whose respiratory function is compromised including those with chronic respiratory illness. Further investigation is encouraged, such as by the use of data from the ongoing study in patients with chronic respiratory illness.

This conclusion of PMDA is going to be discussed at the Expert Discussion.

4.(ii).B.(7) Post-marketing surveillance, etc.

The applicant explained the post-marketing surveillance, etc., of laninamivir octanoate as follows: Of efficacy- and safety-related information obtained from clinical studies submitted for application of laninamivir octanoate, the important identified risks, important potential risks, and important missing information described below will be evaluated. In parallel with the early post-marketing phase vigilance, a use-results survey (target sample size, 3000; planned duration of survey, 1 season [from November to April next year]) is planned to be conducted to grasp the incidence of unknown adverse drug reactions of laninamivir octanoate. Furthermore, from the aspect of the proper use of the product, due to importance in grasping of the emergence of resistant virus strains over years, a specified use-results survey (planned number of strains to be tested, 300 per season for 5 consecutive seasons) is going to be conducted, in which the NA-inhibitory activity of laninamivir octanoate and of oseltamivir phosphate are measured to investigate trends of the emergence of resistant strains by season and by type of influenza virus.

Since the incidence of unknown adverse drug reactions of laninamivir octanoate needs to be learned in the early post-marketing phase, the sample size for the surveillance was determined to be 3000 (collectable size, 100 elderly patients, 1500 pediatric patients, 500 patients aged 10 to 19 years, 150 young children, 100 patients with chronic heart disease, 100 patients with chronic metabolic disease including diabetes mellitus, 100 patients with renal impairment) to detect unknown adverse drug reactions with the incidence of 0.1% with 95% probability.

Important identified risks

There are no identified risks that are classified as "important identified risks." However, abnormal behaviour (psychiatric disorders/neurologic symptom) is listed in the "Clinically significant adverse reactions" section of the package insert of a similar drug oseltamivir phosphate, and is therefore considered an important risk.

Important potential risks
Similarly to zanamivir hydrate, laninamivir octanoate (Inavir) is a dry powder inhaler. The package insert of zanamivir hydrate lists clinically significant adverse reactions including shock, anaphylacticoid symptoms, bronchospasm, dyspnoea, oculomucocutaneous syndrome, toxic epidermal necrolysis, and erythema multiforme (all with unknown frequency). Although none of these adverse drug reactions occurred in clinical studies of laninamivir octanoate, they are considered important potential risks of laninamivir octanoate.

Important missing information
In the clinical studies of laninamivir octanoate in adults, the following high-risk patients were excluded: patients with chronic respiratory illness, patients with chronic renal impairment, and pregnant women; and patients with chronic respiratory illness, patients with chronic heart disease, patients with metabolic disease, patients with renal impairment, and patients with decreased immune function in studies in children. The safety of laninamivir octanoate in these patients was therefore not evaluated. Also, the number of high-risk patients who were eligible for the studies (young children, the elderly, patients with metabolic disease, patients with chronic heart disease, pregnant women) was too small to for safety evaluation.

The results of the clinical studies on laninamivir octanoate did not show any findings suggestive of the aggravation of underlying disease and the progression of influenza virus infection, which are common in high-risk patients. However, these important findings must have been overlooked in the studies in only 94 patients and should be further monitored and assessed after the market launch. Of those who were excluded from the clinical studies, patients with influenza virus infection who have chronic respiratory illness are currently undergoing a clinical study, thus information on the safety of laninamivir octanoate in this population will be available in the future.

The following information on the efficacy of laninamivir octanoate is missing: (a) efficacy against influenza B virus in adults, (b) efficacy in high-risk patients, (c) continued evaluation on the emergence of resistant virus strains, and (d) efficacy against pandemic influenza A/H1N1 virus and highly pathogenic avian influenza A/H5N1 virus.

Besides the above-mentioned tasks planned by the applicant, taking account of the discussions in sections "4.(ii).B.(1) Efficacy, 4.(ii).B.(3) Dosage and administration, 4.(ii).B.(4) Indication, and 4.(ii).B.(5) Clinical positioning," PMDA considers that information should be collected on the following matters through post-marketing surveillance, etc., for further investigation.

- Efficacy of laninamivir octanoate by type and subtype of influenza virus (including the efficacy against A/H3N2 subtype in children)
- The incidence of "dizziness" which was observed only in the laninamivir octanoate groups in the clinical studies
- Measures to ensure successful inhalation

This conclusion of PMDA and other issues for consideration are to 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 inspections 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

Based on the submitted data, PMDA has concluded that the efficacy of Inavir (laninamivir octanoate) in adult and pediatric patients with influenza virus infection has been demonstrated and its safety is acceptable in view of its observed benefits. Inavir is the first product that has demonstrated the clinical efficacy by single dose inhalation and is a new treatment option for influenza virus infection. Inavir thus has clinical significance.

PMDA considers that the following issues should be further investigated.

- Efficacy and safety
- Dosage and administration
- Indication
- Medication education
- Matters to be investigated after the market launch

PMDA considers that Inavir may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

July 7, 2010

I. Product Submitted for Registration

[Brand name]	Inavir Dry Powder Inhaler 20 mg
[Non-proprietary name]	Laninamivir Octanoate Hydrate
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	January 29, 2010

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are described in the following sections.

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 Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

(1) Efficacy

(1).1) Efficacy of laninamivir octanoate in adults

Taking account of the following, PMDA concluded that the efficacy of laninamivir octanoate in adult patients with influenza virus infection was confirmed.

- In the global phase III study (Study CS8958-A-J301) conducted in adult patients with influenza virus infection during the 2008/09 season, the non-inferiority of the laninamivir octanoate group to the oseltamivir phosphate group was demonstrated.

- In the global phase III study (Study CS8958-A-J301), almost all viral strains (644 of 646 samples) isolated from patients with A/H1N1 subtype infection (646 of 999 subjects) were H275Y mutant virus. However, (a) time to alleviation of symptoms in the oseltamivir phosphate group with A/H1N1 subtype infection in this study (Study CS8958-A-J301) (77.5 hours) was similar to that observed in the phase II single dose study (Study CS8958-A-J201) conducted during the 2007/08 season (77.7 hours) (both evaluated in FAS). Also, (b) time to alleviation of symptoms (73.6 hours) in the oseltamivir phosphate group of the global phase III study (Study CS8958-A-J301) was within the range of variation (70.0-87.4 hours) of the time to alleviation of symptoms observed in the past clinical studies of oseltamivir phosphate that were used as the justification for setting the non-inferiority margin in the phase III study, and was relatively shorter (FAS).

Furthermore, after the following review, PMDA concluded that laninamivir octanoate, at least at a dose of 40 mg, is superior to placebo.

- In the global phase III study (Study CS8958-A-J301), time to alleviation of symptoms in the laninamivir octanoate 40 mg group (73.0 hours) was statistically significantly shorter than that in the laninamivir octanoate 20 mg group (85.8 hours), which demonstrated the superiority of laninamivir octanoate, at least at a dose of 40 mg, to placebo.

- In the study in patients aged ≤9 years (Study CS8958-A-J302) conducted during the 2008/09 season, time to alleviation of symptoms was statistically significantly shorter in the

laninamivir octanoate 20 mg group as compared with the oseltamivir phosphate group, and was shorter in the laninamivir octanoate 40 mg group as well, albeit statistically insignificant, which is considered to support the superiority of laninamivir octanoate 40 mg to placebo in adults.

The PMDA's conclusion was generally supported by the expert advisors. At the same time, the expert advisors noted the following comments:

- Although there is no objection to the conclusion on the efficacy of laninamivir octanoate based on the results of the clinical studies, efficacy information should be provided to healthcare professionals while the weakness of the efficacy evidence including unverified superiority of laninamivir octanoate to placebo is born in mind.

- The post-marketing surveillance, etc. should be designed to collect information not only on safety but also on efficacy such as febrile period and change in body temperature.

In response to the comment of the expert advisors on limited evidence of the efficacy of laninamivir octanoate from the aspect of the comparison with placebo, PMDA further conducted the following review.

The applicant's explanation is convincing in terms of difficulty in the conduct of a placebo-controlled study in Japan and the appropriateness of selecting oseltamivir phosphate as comparator for confirmatory studies [see Review Report (1) "4.(ii).B.(1).1).(a) Comparator in confirmatory studies"]. Therefore, efficacy was inevitably evaluated based on the global phase III study (Study CS8958-A-J301) which was a non-inferiority study using oseltamivir phosphate as comparator. In the global phase III study (Study CS8958-A-J301), the non-inferiority margin was defined as 18 hours of difference in the median time to alleviation of symptoms, which is considered to warrant the superiority of laninamivir octanoate to placebo, based on the past clinical studies of oseltamivir phosphate and from the following points of view [see Review Report (1) "4.(ii).B.(1).2) Efficacy evaluation"].

- A value smaller than the difference from placebo (approximately 30 hours) that is suggested from the past clinical studies
- A value smaller than the difference in point estimates in all studies conducted
- A value smaller than the lower limit of 95% confidence interval (19.5 hours) in the combined analysis using the largest number of subjects

The global phase III study (Study CS8958-A-J301) was conducted based on the above premises and has confirmed the non-inferiority of laninamivir octanoate to oseltamivir phosphate. However, approximately 63% to 66% of patients in each treatment group were infected by H275Y mutant virus, which could affect the result in the full analysis set. Therefore, the result of the study needed to be interpreted through careful discussions from different aspects while taking account of the data obtained from all clinical studies. The first discussion was on whether or not oseltamivir phosphate used in the 2008/09 season, which was when H275Y mutant virus was epidemic in Japan, was as effective as that used in clinical studies conducted before the 2008/09 season. However, it failed to reach a clear conclusion due to lack of evidence. PMDA then considered that results of other clinical studies conducted in the 2008/09 season, when the global phase III study was conducted, should be referred to at least for the efficacy evaluation of laninamivir octanoate in the full analysis set [see Review Report (1) "4.(ii).B.(1).2).(a) Efficacy of laninamivir octanoate (adults)"]. In other words, the use of the efficacy data from a comparison with the lower dose group and the study result in children for the evaluation of efficacy in adults was not planned in the original evaluation strategy and was rather exploratory. However, the study data were useful

in a supplementary decision on efficacy made as an interpretation of the non-inferiority study result.

Based on the above review, PMDA concluded that the efficacy of laninamivir octanoate in adult patients with influenza virus infection was confirmed. However, the clinical study results on laninamivir octanoate should be interpreted carefully. Healthcare professionals should be properly informed of insufficiency of efficacy data on laninamivir octanoate such as unclear efficacy against H275Y mutant virus. It should also be advised that a decision on whether the use of laninamivir octanoate is appropriate for the patient be made carefully while drug-resistance information of the epidemic virus is born in mind.

(1).2 Efficacy of laninamivir octanoate in children

Taking account of the following, PMDA concluded that efficacy of laninamivir octanoate was confirmed in pediatric patients with influenza virus infection.

- In the study in patients aged 10 to 19 years (Study CS8958-A-J303), time to alleviation of symptoms tended to be shorter in the laninamivir octanoate 40 mg group than in the laninamivir octanoate 20 mg group, as was the case in adults.

- In the study in patients aged ≤9 years (Study CS8958-A-J302), although it was not designed for statistical testing, time to alleviation of symptoms in the laninamivir octanoate 20 mg group was statistically significantly shorter as compared with the oseltamivir phosphate group, and it was also shorter in the laninamivir octanoate 40 mg group, albeit statistically insignificant.

The above conclusion of PMDA was generally supported by the expert advisors. At the same time, the expert advisors made the following comments:

- There is no objection to the conclusion that, in the study in patients aged ≤9 years (Study CS8958-A-J302), time to alleviation of symptoms was statistically significantly shorter in the laninamivir octanoate 20 mg group as compared with the oseltamivir phosphate group.

- Evidence is too weak to support the selection of 40 mg of laninamivir octanoate as recommended clinical dose instead of 20 mg. Because of limited experience with use in children, it seems to be difficult to conclude that there is no significant difference in the safety of laninamivir octanoate between the dose of 40 mg and 20 mg.

- In the study in patients aged ≤9 years (Study CS8958-A-J302), time to alleviation of symptoms was statistically significantly shorter in the laninamivir octanoate 20 mg group than in the oseltamivir phosphate group, but was not significantly different between laninamivir octanoate 40 mg and laninamivir octanoate 20 mg. These findings should be carefully discussed. If there is no significant difference in the safety of laninamivir octanoate between the dose of 20 mg and 40 mg, the lower dose should be selected.

In response to the comments made by the expert advisors, PMDA further discussed the dosage and administration of laninamivir octanoate in children. Details are described in "(3).1) Dosage and administration of laninamivir octanoate."

(2) Safety

(2).1) Safety of laninamivir octanoate in adults

The results of clinical studies on laninamivir octanoate in adults were reviewed. The laninamivir octanoate groups did not show any serious adverse events. The most common adverse event was "diarrhoea," the incidence of which was similar to that in the oseltamivir phosphate group, with no serious case. Also, in the laninamivir octanoate groups, there were no adverse events with

apparently higher incidence as compared with the oseltamivir phosphate group. Therefore, PMDA has concluded that laninamivir octanoate has no particular safety problem. The comparison between the laninamivir octanoate 20 mg group and the 40 mg group showed neither increased overall incidence of adverse events nor an increase in specific adverse events with an increase in dose. However, since "dizziness" was observed only in the laninamivir octanoate groups, suggesting that the event may be unique to laninamivir octanoate, relevant information should be collected after the market launch and be supplied to clinical practices as appropriate.

The above conclusion of PMDA was supported by the expert advisors. At the same time, the expert advisors made the following comments:

- Possibility that dizziness may have been caused by laninamivir octanoate should be examined in relation to the detailed time course of the symptom and over-time change in the plasma concentration of laninamivir octanoate.

- Possibility that dizziness may be caused by influenza virus infection and the frequency of the event should be found out through literature-based discussion. Whether or not dizziness is related to influenza-associated abnormal behavior should also be carefully investigated.

Taking account of the comments of the expert advisors, PMDA asked for the details of dizziness that occurred during the clinical studies on laninamivir octanoate.

The applicant responded as follows:
A total of 13 patients who experienced dizziness were subject to a further investigation such as on a relationship between the event and the dose of laninamivir octanoate and over-time changes in patient condition including the onset of the event.

The incidence of dizziness was 1.3% (1 of 79 patients) in the laninamivir octanoate 5 mg group, 2.1% (3 of 141 patients) in the laninamivir octanoate 10 mg group, 1.3% (6 of 493 patients) in the laninamivir octanoate 20 mg group, and 0.6% (3 of 519 patients) in the laninamivir octanoate 40 mg group. No dose-dependent trend was observed in the incidence of the event. The symptom was mild or moderate in all affected patients, and no associated symptoms such as nystagmus were observed in any patients.

Time from the administration of laninamivir octanoate to the onset of dizziness was ≤6 days in 11 of 13 patients (on Day 2 in 5 patients). Only 1 patient experienced the event on the day of administration (Day 1). Given that t_{max} of laninamivir octanoate is ≤1 hour and t_{max} of R-125489 is approximately 4 hours, and based on a finding in non-clinical studies that both laninamivir octanoate and R-125489 were little distributed in the central nervous system, it is considered that there is no clear relationship between the plasma concentration of laninamivir octanoate or R-125489 and the occurrence of dizziness. The duration of dizziness was 1 day (until the next day) in 6 patients, 2 days in 2 patients, 5 days in 1 patient, and 7 days in 3 patients (the event occurred intermittently in 1 patient each who had the event for 5 and 7days, respectively).

In the clinical studies on laninamivir octanoate, dizziness did not occur in the oseltamivir phosphate group. However, in clinical studies submitted for the initial approval of oseltamivir phosphate, the event occurred in 1.3% (2 of 154 patients) in the phase III study in Japan and in 2.1% (15 of 724 patients) in the global phase III study. In the global phase III study, dizziness occurred in 3.5% (25 of 716 patients) in the placebo group as well.[62] Although dizziness is not a common associated symptom of influenza virus infection, a report includes dizziness as associated symptom of influenza with the incidences being 1% to 25%, which suggests that

[62] Tamiflu Capsule 75 [summary of product application], Nippon Roche K.K.: December 2000

dizziness may occur as a result of influenza virus infection per se.

Of 13 patients who experienced dizziness, a total of 5 patients had associated adverse events, 1 of which was abnormal dream (1 patient in the laninamivir 40 mg group of a foreign clinical study; the event term entered in CRF was frequent night dream) and was classified in psychiatric disorders of the system organ class. The result suggests that dizziness is not related to influenza-associated abnormal behaviour. In the study in patients aged ≤9 years (Study CS8958-A-J302) and the study in patients aged 10 to 19 years (Study CS8958-A-J303), dizziness was not observed in any patients including those who experienced abnormal behaviour/talk.

Taking account of these findings that dizziness was observed not only in clinical studies on laninamivir octanoate but also in studies on similar drugs and dizziness can be an associated symptom of influenza virus infection, PMDA considers that dizziness is not an adverse event unique to laninamivir octanoate, and therefore there is no particular concern requiring a special alert for now. However, since data from the clinical studies on laninamivir octanoate did not provide sufficient information on dizziness, PMDA advised the applicant that an appropriate investigation on the event should be performed through the post-marketing surveillance.

The applicant accepted it.

(2).2) Safety of laninamivir octanoate in children

The most common adverse event in children treated with laninamivir octanoate was "diarrhoea" as with adults, but no serious diarrhoea was observed. The incidence was high as compared with the oseltamivir phosphate group but was similar to that in adults in the laninamivir octanoate group.

Adverse events of pyrexia, bronchitis, gastroenteritis, delirium, abnormal behaviour, epistaxis, upper respiratory tract inflammation were observed more frequently in children than in adults, but none of these were serious. There was no specific increase in abnormal behaviour/talk in children treated with laninamivir octanoate. From these results, PMDA concluded that laninamivir octanoate does not pose particular safety problem in children.

However, given the fact that psychiatric disorder/neurologic symptoms such as abnormal behaviour was reported in patients with influenza virus infection who were treated with oseltamivir phosphate, a drug similar to laninamivir octanoate, although without a causal relationship between the drug and the event, PMDA considered that the risk of psychiatric disorder/neurologic symptoms such as abnormal behaviour with laninamivir octanoate cannot be completely ruled out. Therefore caution should be given on the risk as with other antiviral drugs against influenza and relevant information should be further collected after the market launch.

The above conclusion of PMDA was supported by the expert advisors. At the same time, the expert advisors noted the following comments:

- Psychiatric disorder/neurologic symptoms such as abnormal behaviour observed in 9 patients in the clinical studies on laninamivir octanoate should be accurately evaluated based on time-series details and situations grasped. Also, relevant information should be further collected carefully after the market launch.

- Although there were no serious adverse events, delirium, abnormal behaviour, etc., were observed more frequently in children than in adults. Careful observation should be made to determine whether these were associated symptoms of influenza virus infection or were induced by laninamivir octanoate, as with other antiviral drugs against influenza.

Based on the above comments made by the expert advisors, PMDA asked the applicant to explain the details of abnormal behaviour, etc., observed in 9 patients in the clinical studies of laninamivir octanoate.

The applicant responded as follows:
In patients who presented with abnormal behaviour/talk, time from the administration of laninamivir octanoate or influenza virus infection to the presentation of abnormal behaviour/talk and a temporal relationship between change in sleep or body temperature and the presentation of abnormal behaviour/talk were investigated.

Times from the end of the administration of laninamivir octanoate to the presentation of abnormal behaviour/talk varied among patients, ranging from approximately 1 to 34 hours, and showed no clear relationship with t_{max} values of laninamivir octanoate (≤1 hour) and R-125489 (approximately 4 hours). Meanwhile, all affected patients presented abnormal behaviour/talk during sleep or immediately after awakening. Although body temperature was not measured at the time of the presentation of abnormal behaviour/talk, it is estimated to be approximately ≥38°C based on the body temperature measured before and after presentation. These findings show no clear relationship between laninamivir octanoate and abnormal behaviour/talk and rather suggest a relationship of pyrexia and sleep to abnormal behaviour/talk.

Based on the review, PMDA considers that laninamivir octanoate does not pose particular safety problem in children for now. However, adequate information should be collected after the market launch on the occurrence of psychiatric disorder/neurologic symptoms such as abnormal behaviour for a close investigation. A relationship between laninamivir octanoate and symptoms such as abnormal behaviour should be investigated based on the available data, and relevant information should be supplied to clinical practices as appropriate.

(3) Dosage and administration

(3).1) Dosage and administration of laninamivir octanoate

PMDA concluded that there is no harm in defining dosage and administration in adults as single dose inhalation of laninamivir octanoate 40 mg based on the results of the global phase III study (Study CS8958-A-J301) [see Review Report (1) "4.(ii).B.(3).1) Dosage and administration of laninamivir octanoate" and Review Report (2) "(1).1) Efficacy of laninamivir octanoate in adults"]. This conclusion was supported by the expert advisors.

In the study in patients aged ≤9 years (Study CS8958-A-J302), the efficacies of laninamivir octanoate were similar between the doses of 20 mg and 40 mg. However, an efficacy endpoint of viral titer was low in some patients in the laninamivir octanoate 40 mg group, the median time to alleviation of symptoms of influenza B virus infection tended to be slightly shorter in the laninamivir octanoate 40 mg group than in the 20 mg group, and the incidence of adverse events did not show a dose-dependent increase. PMDA concluded that there was no harm in defining the dosage and administration of laninamivir octanoate in children as 40 mg single dose inhalation, the same dosage regimen as in adults.

The expert advisors made the following comments on the dosage and administration of laninamivir octanoate in children:

- In the study in patients aged ≤9 years (Study CS8958-A-J302), time to alleviation of symptoms in the laninamivir octanoate 20 mg group was statistically significantly shorter than in the oseltamivir phosphate group, whereas that in the laninamivir octanoate 40 mg group did not show a decreasing trend as compared with the laninamivir octanoate 20 mg group. Taking account of these results, the following findings were presented by the applicant as the rationale for the recommended clinical dose of laninamivir octanoate as 40 mg, which, however, are

considered not strong enough: (i) a secondary efficacy endpoint of viral titer was lower in the laninamivir octanoate 40 mg group, (ii) the median time to alleviation of symptoms caused by influenza B virus tended to be slightly shorter in the laninamivir octanoate 40 mg group than in the 20 mg group, and (iii) the incidences of adverse events did not show a dose-dependent increase.

- In general, when different doses demonstrate similar efficacy, the lower dose should be selected because of its preferred lower exposure level. At present, due to lack of experience with the use of laninamivir octanoate in children, it is difficult to conclude that there is no significant difference in the safety of laninamivir octanoate between the doses of 20 mg and 40 mg. Therefore, the recommended dose in children should be 20 mg instead of 40 mg.

- Since the use of oseltamivir phosphate as comparator in adolescents is restricted aged 10 to 19 years in Japan, separate clinical studies on laninamivir octanoate were conducted for patients aged ≤9 years and for patients aged 10 to 19 years. Considering adequate body size of adolescents aged 10 to 19 years and the result of the clinical study showing decreased time to alleviation of symptoms in the laninamivir octanoate 40 mg group as compared with the laninamivir octanoate 20 mg group, it is appropriate to define the recommended dose of laninamivir octanoate in this age group as 40 mg as with adults.

In response to the above comments of the expert advisors, PMDA performed further reviews as described below.

Due to the age restriction on the use of oseltamivir phosphate as comparator, separate clinical studies were conducted for 2 age groups of children. In the study in patients aged ≤9 years (Study CS8958-A-J302), the primary efficacy endpoint of time to alleviation of symptoms was similar between the laninamivir octanoate 20 mg group and the 40 mg group, and statistically significantly shorter in the laninamivir octanoate 20 mg group than in the control group. On the other hand, in the study in patients aged 10 to 19 years (Study CS8958-A-J303), time to alleviation of symptoms tended to be shorter in the laninamivir octanoate 40 mg group than in the 20 mg group, as was observed in the study in adults. The evidence obtained from clinical studies on laninamivir octanoate suggests a difference in the optimal dose of laninamivir octanoate between patients aged ≤9 years and patients aged 10 to 19 years.

The results of the secondary efficacy endpoints (viral titer on Day 3, time to alleviation of symptoms of influenza B virus) in the study in patients aged ≤9 years (Study CS8958-A-J302) were presented by the applicant as evidence to support the recommended dose of laninamivir octanoate 40 mg for pediatric use. However, all secondary endpoints including others failed to demonstrate a consistent relationship between dose and efficacy, and thus are not sufficient to serve as grounds for the superiority of the dose of 40 mg to 20 mg in the efficacy of laninamivir octanoate. Time to alleviation of symptoms caused by influenza B virus infection tended to be slightly shorter in the laninamivir octanoate 40 mg group than in the 20 mg group. Nonetheless, each treatment group of the study in children aged ≤9 years had only approximately 10 patients with influenza B virus infection, precluding a clear conclusion on the superiority in the efficacy. For A/H1N1 subtype on the other hand, it was confirmed that time to alleviation of symptoms tended to be slightly shorter in the laninamivir octanoate 20 mg group than in the 40 mg group, and the similar trend was observed with A/H3N2 subtype as well.

Therefore, taking account of the results of the study in patients aged ≤9 years (Study CS8958-A-J302), PMDA considered that the efficacy of laninamivir octanoate is expected be comparable between the 20 mg group and the 40 mg group in patients aged ≤9 years. Also considering the expert advisors' comment that while the incidence of adverse events did not increase in a dose-dependent manner, the experiences in around 60 children aged ≤9 years in each treatment group

does not provide strong evidence for a relationship between safety and dose, PMDA concluded that it is appropriate to select laninamivir octanoate 20 mg as recommended dose instead of 40 mg, in the situation where the efficacy of the two doses is similar.

On the other hand, in the study in patients aged 10 to 19 years (Study CS8958-A-J303), 65.8% (79 of 120) of patients were 10 to 12 years old, 23.3% (28 of 120) 13 to 15 years old, and 10.8% (13 of 120) 16 to 19 years old, with the majority of patients being <16 years. In the clinical study enrolling patients in these age groups, time to alleviation of symptoms was confirmed to be shorter in the laninamivir octanoate 40 mg group than in the 20 mg group as was the case in adults, and PMDA therefore considers that laninamivir octanoate 40 mg is the appropriate recommended dose also for children aged ≥10 years.

Based on the above review, the dosage and administration of laninamivir octanoate is defined as a single dose of 20 mg in children aged ≤9 years and single dose inhalation of 40 mg in children aged 10 to 19 years. The Expert Discussion brought up a possible risk of making healthcare professionals confused by different dosage and administration by age group (<9 years or ≥10 years), but no particular concern was raised by the expert advisors.

(3).2 Dosage and administration of laninamivir octanoate in patients with renal impairment

Taking account of the following 2 points, PMDA concluded that there is no harm in defining dosage and administration of laninamivir octanoate in patients with renal impairment as single dose inhalation of 40 mg, as with patients with normal renal function: (a) in patients with severely decreased renal function (CL_{CR} <30 mL/min), C_{max} and $AUC_{0\text{-}inf}$ of the active metabolite of laninamivir octanoate R-125489 increased approximately 1.9 and 5 fold, respectively. However, no significant safety problem was observed either in the clinical study in healthy subjects with up to 120 mg of laninamivir octanoate administered by single dose inhalation or in another study with laninamivir octanoate of a total dose of 200 mg administered by multiple inhalations (40 mg twice daily for a total of 5 doses), and (b) when a relationship between renal function and safety was evaluated in patients enrolled in clinical studies of laninamivir octanoate who were stratified by estimated glomerular filtration rate (eGFR), although the incidence of adverse events was slightly higher in patients with low eGFR value (< 60 mL/min/1.73 m^2) than in patients with normal renal function, a dose-dependent change in the incidence of adverse events was unclear, suggesting no significant safety problem. However, due to limited experience in the administration of laninamivir octanoate in patients with renal impairment and no experience in patients with severely decreased renal function, PMDA concluded that safety information of laninamivir octanoate in patients with renal impairment should be collected after the market launch.

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

(3).3 Timing of administration

PMDA concluded that the package insert should include a statement to the effect that laninamivir octanoate should be administered immediately after the onset of symptoms and that there is limited experience in the administration of the drug >36 hours after the onset of symptoms , based on the following 2 points: (a) the results of the global phase III study (Study CS8958-A-J301) and the study in patients aged ≤9 years (Study CS8958-A-J302) showed no impact of the difference in time from the onset of influenza to the end of treatment on efficacy in patients who completed the treatment within 36 hours after onset. However, given the mechanism of action of laninamivir octanoate against influenza virus infection, laninamivir octanoate should be administered as early as possible, and (b) no significant difference in efficacy was observed between the subgroup of patients who completed the treatment >36 hours after onset and the entire population, but the number of subjects was small in the subgroup.

The expert advisors made the following comments on the above conclusion of PMDA:

- As the package inserts of similar drugs note to the effect that "there are no data that support efficacy in patients who start treatment ≥48 hours after onset of symptoms," in clinical practices "48 hours" is well known critical timing for starting treatment with antiviral drugs against influenza. Therefore, noting only on the lack of experience in treatment with the drug >36 hours after onset of symptoms in the package insert, etc., of laninamivir octanoate may confuse healthcare professionals. Strong grounds should be provided for the critical time point of "36 hours".

- Information on the relationship between the efficacy of laninamivir octanoate and time from the onset of symptoms to the end of treatment should be collected through post-marketing surveillance.

Taking account of the above comments of the expert advisors, PMDA further performed the following reviews.

PMDA confirmed that, in most clinical studies of similar drugs of oseltamivir phosphate and zanamivir hydrate including those in Japan, the time from the onset of influenza symptoms was defined as ≤36 hours, whereas the package insert, etc., of these drugs warn that treatment should be started within "48 hours" after onset of symptoms, and textbooks and guidelines also note that NA inhibitors should be administered within "48 hours" after the onset of symptoms.

In terms of laninamivir octanoate, (a) "≤36-hours after the onset of influenza symptoms" is not time from the onset of symptoms to the start of treatment but was defined as time to consent to the participation in the study, (b) there were a total of 37 subjects in the subgroup of patients who received laninamivir octanoate and completed the treatment ≥36 hours after onset of symptoms (maximum time from the onset, 46.8 hours), and there was no significant difference in the efficacy of laninamivir octanoate between the subgroup and the entire study population [see Review Report (1) "4.(ii).B.(1).3).(b) Efficacy by time of disease onset"]. Given that laninamivir octanoate is another NA inhibitor, PMDA considers that the package insert, etc., of laninamivir octanoate should also note to the effect that the drug should be administered as early as possible after onset and that there are no data that support the efficacy of laninamivir octanoate in patients who start treatment ≥48 hours after onset.

Based on the above, PMDA has concluded that the dosage and administration of laninamivir octanoate should be defined as shown below. The package insert should also note to the effect that "20 mg of laninamivir octanoate should be administered with 1 inhaler, and 40 mg with 2 inhalers."

Adults:	Laninamivir octanoate 40 mg is administered by inhalation as a single dose.
Children aged <10 years:	Laninamivir octanoate 20 mg is administered by inhalation as a single dose.
Children aged ≥10 years:	Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

(4) Indication

(4).1) Indication of laninamivir

Based on the study results submitted, PMDA has concluded that the proposed indication of "influenza A or B virus infection" is acceptable.

The above conclusion of PMDA was supported by the expert advisors. At the same time, the expert advisors made the following comments:

- Investigations of A/H3N2 subtype and type B viruses in clinical studies of laninamivir octanoate were based on only a small number of patients with the said virus type and subtype, and no study data are available on the pandemic A/H1N1 virus which has been epidemic since 2009. This information should be provided to healthcare professionals.

- Healthcare professionals need to be informed that the efficacy of an antiviral drug against influenza is not equal in all types and subtypes of the influenza virus and varies depending on the type or subtype of virus spreading at the time of treatment in association with the emergence of drug-resistant strains. Therefore, the information on the efficacy of laninamivir octanoate by virus type and subtype obtained from the clinical studies of laninamivir octanoate should be provided to healthcare professionals, and further information should be collected after the market launch to be provided to clinical practices.

PMDA instructed the applicant (i) to provide healthcare professionals with information on the distribution of epidemic strains during the seasons when clinical studies of laninamivir octanoate were conducted (including information on oseltamivir-resistant virus and pandemic A/H1N1 virus) as well as information on the efficacy of the drug by virus type and subtype that was investigated in the clinical studies on laninamivir octanoate (with a precaution on a small number of patients with A/H3N2 subtype or type B investigated), and (ii) to design the post-marketing surveillance so that information can be obtained not only on the safety but also on the efficacy of laninamivir octanoate by type and subtype of influenza virus, and to immediately provide clinical practices with information once become available.

The applicant responded that it will update information materials with obtained information accordingly and provide them to healthcare professionals in an appropriate manner, while bearing the above instructions in mind.

PMDA accepted the response of the applicant.

(4).2) Administration of laninamivir octanoate to high-risk patients

Based on the safety review in high-risk patients enrolled in clinical studies, PMDA concluded that there is no particular problem at present. However, due to the exclusion of high-risk patients with renal impairment, chronic respiratory illness, pregnant or lactating women, or decreased immune function from all clinical studies, information for safety evaluation in these patient groups is not available. Therefore, PMDA concluded that the package insert, etc. should include the precautions about the availability of limited safety information of laninamivir octanoate in these high-risk patients.

A clinical study reported 1 pregnant woman who received laninamivir octanoate gave birth to a neonate with a serious adverse event of malformations multiple (cerebral ventricle dilatation during fetal phase, brain malformation, low set ears, and micrognathia confirmed after birth) [see Review Report (1) “4.(ii).B.(2).3).(d) Safety in pregnant women and fetuses”]. However, given the low risk of teratogenicity as judged from the results of nonclinical studies [see Review Report (1) “3.(iii).A.(5) Reproductive and developmental toxicity”], and a temporal relationship between the formation stage of these organs and the administration of laninamivir octanoate (Gestation week 15, the less sensitive stage), a causal relationship between the multiple malformations that were observed primarily in the central nervous system and laninamivir octanoate is not clear, and therefore multiple malformations may have been a coincidental event [see Review Report (1) “4.(ii).B.(2).3).(d) Safety in pregnant women and fetuses”]. Therefore, PMDA considers that the administration of laninamivir octanoate is not necessarily contraindicated in pregnant women

without exception based on the reported case, but, as with similar drugs, it should be cautioned that laninamivir octanoate should not be used in pregnant women or women who may be pregnant unless the expected therapeutic benefit outweighs the possible risk associated with treatment.

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

PMDA instructed the applicant to inform healthcare professionals of the fact that neither the efficacy nor safety of laninamivir octanoate has been established in high-risk patients because of limited use experience in this patient group in clinical study of laninamivir octanoate, and to provide the result of the ongoing study in high-risk patients (patients with chronic respiratory illness) to healthcare professionals in a timely manner.

The applicant accepted the instructions.

(4).3) Other

Laninamivir octanoate prophylactic use is also now under development and the efficacy of the drug in prophylactic use has not been established for now. This should be highlighted in the package insert.

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

(5) Clinical positioning

Laninamivir octanoate is an NA inhibitor that was shown to be non-inferior to oseltamivir phosphate in the global phase III study (Study CS8958-A-J301). Therefore, PMDA considers that laninamivir octanoate is effective for the treatment influenza virus infection as with the similar drugs. Also, laninamivir octanoate is formulated for a single dose regimen and is therefore of clinical significance as a new treatment option for influenza virus infection.

The preparation of guidelines for the proper use of laninamivir octanoate, including the clinical positioning of laninamivir octanoate, should be expedited in collaboration with relevant academic societies, etc. for distribution to healthcare professionals in clinical practice. Close monitoring on the emergence of virus strains resistant to laninamivir octanoate or other NA inhibitors should be continued after the market launch.

The expert advisors pointed out the weakness of the grounds for the superiority of laninamivir octanoate to the similar drugs in efficacy against resistant virus strains and noted that the efficacy against resistant virus strains should be determined based on the efficacy evaluation by type and subtype of influenza virus that is to be conducted after the market launch. However, they supported the above conclusion of PMDA.

(6) Measures to ensure correct inhalation

Since Inavir (laninamivir octanoate) is a powder form drug to be inhaled, PMDA considers that the drug should be administered while paying attention to the following: (a) patients must receive education to learn the proper inhalation technique from healthcare professionals. Patients also must strictly adhere to instructions on the use of the drug so that the single-dose regimen is optimized, (b) any difficulties in adherence to the proper inhalation technique should be monitored after the market launch and identified problems should be addressed promptly in collaboration with medical institutions, etc. and (c) in children, as with the similar inhaled drugs, laninamivir octanoate may be prescribed on a patient-by-patient bases regardless of his or her age group at the physician's discretion on the patient's competency in inhalation of the drug. For this purpose, the package insert, etc. should highlight that "Inavir should be administered only to children who are considered competent in the proper use of the product" along with the relevant

information including the age range of children to whom laninamivir octanoate was administered in clinical studies.

The above conclusion of PMDA was supported by the expert advisors. At the same time, the following comments were made by the expert advisors:

- Since Inavir (laninamivir octanoate) is an inhalation powder and is formulated for a single-dose regimen, inadequate inhalation technique results in poor efficacy of the drug. Physicians and pharmacists should be informed of the importance of patient education on the proper inhalation technique to their patients when prescribing laninamivir octanoate.

- To ensure the patient's competence in inhaling Invavir, the patient should inhale the drug in the presence of the physician upon diagnosis, rather than taking the drug alone after learning the inhalation technique and receiving the drug.

- Particularly in clinics and emergency outpatient units for children, laninamivir octanoate is expected to be administered upon diagnosis. Therefore, the clinical positioning of laninamivir octanoate in children is considered different from the similar drugs in terms of the simultaneity of diagnosis and the administration of the drug.

- The youngest patient treated in clinical studies of laninamivir octanoate was 3 years old. No efficacy, safety, or inhalation feasibility was investigated in children younger than 3 years.

- Inhaler A was employed in all clinical studies of laninamivir octanoate in children, and TwinCaps is to be used by patients only after the market launch of Inavir. Children's competence in the safe and effective use of TwinCaps needs to be verified.

- Materials for adequate education on the proper inhalation technique should be prepared and distributed to healthcare professionals and patients upon the market launch.

Based on these comments of the expert advisors, PMDA instructed the applicant (a) to expedite the preparation of education materials and distribute them to clinical practices (patients, healthcare professionals), (b) to inform healthcare professionals that laninamivir octanoate should be administered only to those children who are considered competent in properly handling the drug product and that healthcare professionals also need to be informed of the age group of children to whom laninamivir octanoate was administered in clinical studies, and (c) because of the lack of experience in using TwinCaps, to monitor the competence in the use of TwinCaps and closely investigate possible problems in the inhalation of laninamivir octanoate particularly in young children, and take an immediate action to the identified problem, if any.

The applicant responded that PMDA's instructions were followed to prepare information materials, through which appropriate information would be provided to healthcare professionals in clinical practice.

PMDA accepted the response of the applicant.

(7) Post-marketing investigations

The applicant plans to conduct a use-results survey (target sample size, 3000; planned survey period, 1 season from November to April next year) to understand the incidences of unknown adverse reactions of laninamivir octanoate. The applicant also plans to conduct a specified use-results survey to investigate trends in the emergence of resistant strains by season and type of influenza virus, by measuring the NA-inhibitory activities of laninamivir octanoate and

oseltamivir phosphate (planned number of strains to be tested, 300 per season for 5 consecutive seasons).

PMDA considers that the post-marketing surveillance, etc., should also focus on the following 3 matters in addition to the applicant's intended objectives:

- The result of the investigation on the efficacy of the drug product by viral type [see Review Report (1) "4.(ii).B.(1).3).(a) Efficacy by type of influenza virus"] showed prolonged time to alleviation of symptoms in the laninamivir octanoate group as compared with the oseltamivir phosphate group and the absence of a dose-dependent relationship, failing to produce evidence demonstrating the efficacy of laninamivir octanoate in the treatment of influenza infection of A/H3N2 subtype in children. Therefore, information should be further collected after the market launch on the efficacy of Inavir in children by viral type and subtype including A/H3N2 subtype.

- The incidence of an adverse event of "dizziness," which was observed only in the laninamivir octanoate group in clinical studies, should be investigated.

- After the market launch of Inavir, facts in the inhalation of laninamivir octanoate by patients and associated problems, if any, should be clarified. The findings are to be reflected in future education.

The conclusion of PMDA was supported by the expert advisors. The expert advisors also made the following comments:

- Because the results of clinical studies did not produce strong enough evidence to support the efficacy of laninamivir octanoate, efficacy data as well as safety data should be further collected after the market launch.

- The extent of decrease in the influenza viral load after the administration of laninamivir octanoate should be clarified.

- The target patients of the use-results survey should include patients who have decreased immune function.

Based on these comments of expert advisors, PMDA instructed the applicant to take into consideration the following in the conduct of post-marketing surveillance. Since the extent of decrease in viral load after the administration of laninamivir octanoate has also been investigated in the clinical studies, the data should be included in the information materials to be provided to clinical practices.

- The use-results survey should include patients who have decreased immune function as study subjects.

- The post-marketing surveillance should be designed for the evaluation of not only the safety but also the efficacy of laninamivir octanoate.

- A possible risk of laninamivir octanoate-induced psychiatric disorders/neurologic symptoms such as abnormal behavior cannot be completely ruled out. Therefore, the incidences of said events should be closely investigated.

The applicant responded that (i) in the post-marketing surveillance, etc., information on the efficacy of Inavir will be collected by type and subtype of influenza virus, and that (ii) all kinds

of efforts, including the modification of the survey form, will be made so as to collect as much information as possible.
PMDA accepted the response of the applicant.

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 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, no particular problems were found. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

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

A 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 5.3.5.1-3, 5.3.5.1-5, 5.3.5.1-6). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the results of the above review, PMDA has concluded that Inavir (laninamivir octanoate) may be approved with the following indications, dosage and administration. 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]
Treatment of influenza virus A or B infection

[Dosage and administration]

Adults:	Laninamivir octanoate 40 mg is administered by inhalation as a single dose.
Children aged <10 years:	Laninamivir octanoate 20 mg is administered by inhalation as a single dose.
Children aged ≥10 years:	Laninamivir octanoate 40 mg is administered by inhalation as a single dose.

(The underlined parts denote changes after submission.)