Report on the Deliberation Results

May 8, 2019

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

Brand Name	Inavir for Inhalation Suspension 160 mg Set
Non-proprietary Name	Laninamivir Octanoate Hydrate (JAN*)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	July 10, 2018

Results of Deliberation

In its meeting held on April 19, 2019, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 4 years. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

April 8, 2019
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Inavir for Inhalation Suspension 160 mg Set
Non-proprietary Name	Laninamivir Octanoate Hydrate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	July 10, 2018
Dosage Form/Strength	Combination product consisting of a powder for nebulizer suspension containing 166.1 mg of laninamivir octanoate hydrate (equivalent to 160 mg of laninamivir octanoate) in 1 vial and a nebulizer
Application Classification	Prescription drug, (5) Drug in a new dosage form
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with influenza A or B virus infection, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication
Treatment of influenza A or B virus infection

Dosage and Administration
The recommended dosage for both adults and pediatrics is 160 mg of laninamivir octanoate, suspended in 2 mL of Isotonic Sodium Chloride Solution (physiological saline solution), Japanese Pharmacopoeia grade, and then administered as a single dose by inhalation via a nebulizer.

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

Attachment

Review Report (1)

February 15, 2019

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

Product Submitted for Approval

Brand Name	Inavir for Inhalation Solution 160 mg Set (name proposed at the submission of marketing application)
Non-proprietary Name	Laninamivir Octanoate Hydrate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	July 10, 2018
Dosage Form/Strength	Combination product consisting of a powder for nebulizer suspension containing 166.1 mg of laninamivir octanoate hydrate (equivalent to 160 mg of laninamivir octanoate) in 1 vial and a nebulizer
Proposed Indication	Treatment of influenza A or B virus infection

Proposed Dosage and Administration

The recommended dosage for both adults and pediatrics is 160 mg of laninamivir octanoate, suspended in 2 mL of Isotonic Sodium Chloride Solution (physiological saline solution), Japanese Pharmacopoeia grade, and then administered as a single dose by inhalation via a nebulizer.

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List of Abbreviations

See Appendix.

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

Laninamivir Octanoate Hydrate (hereinafter referred to as laninamivir octanoate) is an influenza antiviral drug discovered by Daiichi Sankyo Company, Limited. Laninamivir octanoate is metabolized to its active metabolite R-125489, which suppresses the replication of influenza A and B viruses by selectively inhibiting neuraminidase present on the surface of these viruses. In Japan, the dry powder inhaler (DPI) formulation containing laninamivir octanoate as its active ingredient (brand name: Inavir Dry Powder Inhaler 20 mg) was approved in September 2010 for the treatment of influenza A or B virus infection and, in December 2013 and August 2016, new indications and dosage and administration for prophylactic use were approved additionally.

The approved laninamivir octanoate dry powder inhaler formulation (hereinafter referred to as "laninamivir octanoate DPI") is difficult to use in pediatric patients aged <5 years, patients with severely compromised pulmonary function due to concurrent respiratory disease (e.g., bronchial asthma, chronic obstructive pulmonary disease [COPD]), and patients who cannot understand the procedure for inhalation. In addition, laninamivir octanoate DPI contains lactose hydrate as an excipient, and physicians must therefore carefully decide whether to use the product in patients with a history of hypersensitivity to dairy products. In order to overcome these problems, the applicant initiated the development of an inhalation suspension formulation of laninamivir octanoate that can be inhaled by spontaneous breathing, and then developed a combination product set composed of the formulation and a single-use nebulizer for patients' convenience and for infection control in clinical practice. Inavir for Inhalation Suspension is expected to offer a new treatment option for patients with influenza A or B virus infection who are unable to use the approved laninamivir octanoate DPI.

Recently, results of the Japanese studies (Study CS8958-B-J310 [Study J310] and Study CS8958-B-J311 [Study J311]) in patients with influenza virus infection became available, which confirmed the efficacy and safety of Inavir for Inhalation Suspension for the treatment of influenza A or B virus infection. Based on these results, an application was submitted to obtain the marketing approval of Inavir for Inhalation Suspension 160 mg Set for the treatment of influenza A or B virus infection.

Laninamivir octanoate is not approved in foreign countries as of January 2019.

In the course of the review of the marketing application submitted, the proposed brand name of laninamivir octanoate was changed from "Inavir for Inhalation Solution 160 mg Set" to "Inavir for Inhalation Suspension 160 mg Set."

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

The drug substance laninamivir octanoate hydrate is identical to the drug substance used for the manufacture of "Inavir Dry Powder Inhaler 20 mg," and no new data were submitted.

2.1 Drug product

2.1.1 Description and composition of drug product and formulation development

The drug product is a combination product consisting of a lyophilized powder for suspension containing 166.1 mg of laninamivir octanoate hydrate (equivalent to 160 mg of laninamivir octanoate) and a nebulizer[1)] supplied with the drug product. The lyophilized powder contains tyloxapol as an excipient. The lyophilized powder should be suspended in Isotonic Sodium Chloride Solution (physiological saline solution), Japanese Pharmacopoeia grade. The nebulizer supplied with the drug product is a non-heated nebulizer made of polypropylene (except the valve made of silicone), which is designed to be connected to a mask.[2)] The drug product is packaged in a carton box.

The drug product aims to ensure that laninamivir octanoate reaches the trachea and lungs to a similar extent to the amount of drug delivered by the approved product "Inavir Dry Powder Inhaler 20 mg" (Review Report of Inavir Dry Powder Inhaler 20 mg [dated July 7, 2010]). For this purpose, the drug product is designed to allow the delivery of a constant amount of the drug particles ≤[redacted] μm in diameter to the target sites via a nebulizer in patients in each age group [see Section 6.R].

2.1.2 Manufacturing process

The drug product is manufactured through a process comprised of the test for [redacted], packaging/labeling, and product inspection/storage. Among these steps, [redacted] and [redacted] are identified as the critical steps. In-process control parameters and action limits have been established for both critical steps.

A quality-by-design approach was applied to the following studies to formulate the quality control strategy (Table 1):

- Identification of critical quality attributes
- Identification of critical process parameters based on the quality risk assessment by failure mode effects analysis

Table 1. Outline of quality control strategy for the drug product

Critical quality attribute	Controls
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.1.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (liquid chromatography/ultraviolet-visible spectrophotometry), uniformity of dosage unit (content uniformity [liquid chromatography]), fine particle dose[3)] (liquid chromatography), microbial limit, and assay (liquid chromatography).

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1) A compressor to which a nebulizer is connected needs to be obtained separately.
2) A nebulizer with a face mask has been developed that can be used by children aged <5 years and elderly patients who have difficulty in using laninamivir octanoate DPI.
3) [redacted]

2.1.4 Stability of drug product

Table 2 shows the stability studies conducted on the drug product. A photostability testing showed that the drug product is photostable.

Table 2. Stability studies on drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot-scale batches	25 ± 2°C	60 ± 5% RH	A glass vial + a butyl rubber stopper + an aluminum/ polypropylene cap	24 months
Accelerated testing	3 pilot-scale batches	40 ± 2°C	75 ± 5% RH		6 months

On the basis of the above, the shelf life of 36 months has been proposed for the drug product when placed in a glass vial which is tightly sealed with a butyl rubber stopper and an aluminum/polypropylene cap, and stored at room temperature. The shelf life was determined in accordance with the "Guideline on the Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). Long-term testing will be continued for up to 36 months.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following reviews, PMDA has concluded that the quality of the drug substance, the drug product, and the nebulizer supplied with the drug product is controlled adequately.

2.R.1 Cut-off diameter used in the definition of the fine particle dose of the drug product

The applicant's explanation about the justification for defining the fine particles of the drug product as particles ≤[redacted] μm in diameter:

The fine particle dose of Inavir Dry Powder Inhaler 20 mg is defined as the "amount of laninamivir octanoate [redacted]" when the amount of drug particles distributed in each stage was measured under the condition corresponding to the in-flow rate of [redacted] L/min using an Andersen cascade impactor[4] (see Figure 1), as listed in "6.15 Aerodynamic Particle Size Distribution Measurement for Inhalations" in Supplement I to the Japanese Pharmacopoeia 17th Edition. No specific value is defined for [redacted]. Since the instrument is designed such that larger particles are separated into the impactor stage with a lower number, the particle size[5] [redacted] is considered to be the maximum size (cut-off diameter) of fine particles included in the definition of the fine particle dose for laninamivir octanoate DPI. The specific cut-off diameter for each stage is known to vary depending on the conditions of the aspiration flow rate at the time of measurement. There is no published report on the cut-off value under the flow rate of [redacted] L/min used in this study. However, taking account of the report on the cut-off diameter (4.7 and 3.2 μm) in stage 3 at the aspiration flow rate of 28.3 L/min and 60 L/min, respectively (*J Aerosol Med.* 2003;16(4):341-77), [redacted], and the cut-off diameter at the aspiration flow rate of [redacted] L/min was calculated to be [redacted] μm. Based on this result, the fine particle dose of the drug product is defined as "the amount of laninamivir octanoate inhalation suspension with a particle

4) The fine particles of the drug powder sucked into the Andersen cascade impactor reach any of 12 parts that constitute the impactor (mouthpiece adapter, pre-separator, induction port, stages 0 to 7, and filter) according to the particle size. The smaller the size of the drug particle, the large the number of the stage it reaches.

5) Maximum particle size [redacted]

size of ≤[redacted] μm.[6)]" Taking account of the description in section "6.15 Aerodynamic Particle Size Distribution Measurement for Inhalations" in Supplement I to the Japanese Pharmacopoeia 17th Edition that "Calculate the fine particle dose (FPD) by interpolation of the mass of the active substance less than or equal to 5 μm. Alternatively, it is possible to determine the FPD as the mass of the active substance deposited on the stages corresponding to the cut-off diameter of 5 μm and less," [redacted] was not included in the definition of the fine particle dose of the drug product.

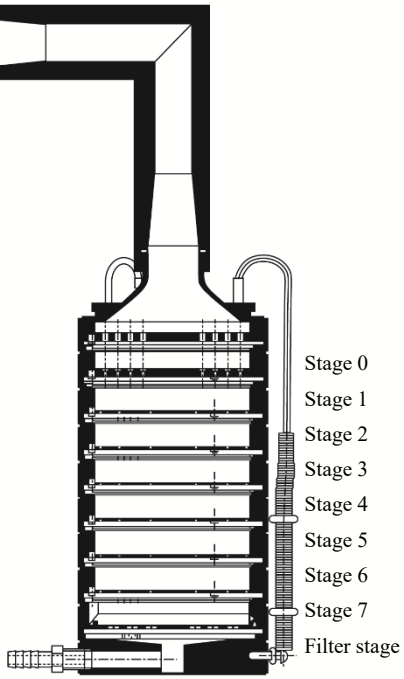

Figure 1. Andersen cascade impactor
(Supplement I to the Japanese Pharmacopoeia 17th Edition)

6) For the drug product, the particle size was calculated using the next generation impactor which is considered to show correlation with Andersen cascade impactor in the aerodynamic particle size (*AAPS PharmSciTech*. 2017;18:646-53) (see Figure 2).

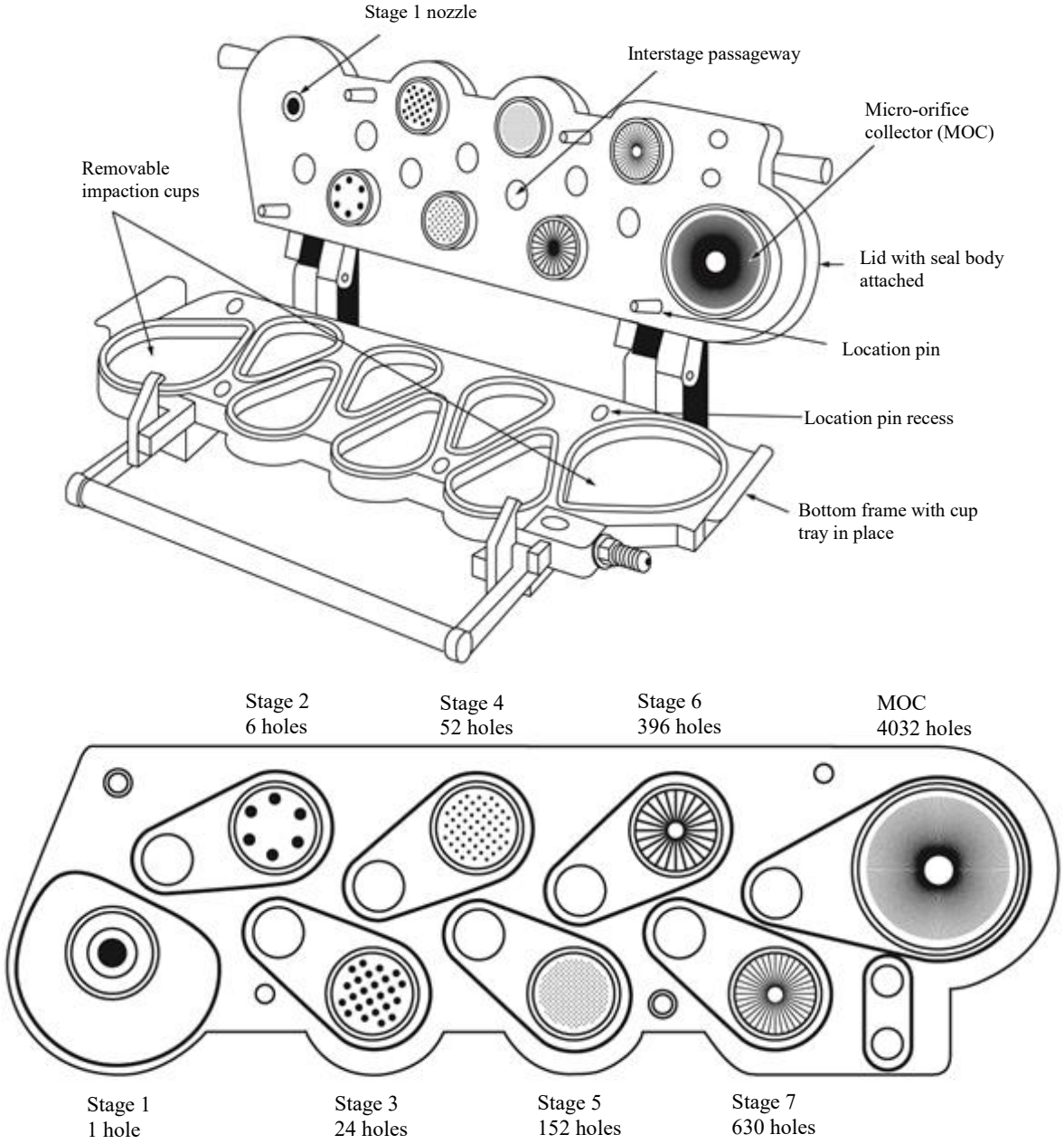

Figure 2. Next generation impactor
(Supplement I to the Japanese Pharmacopoeia 17th Edition)

PMDA considered that there are no particular problems in the applicant's explanation.

2.R.2 Comparability assessment of inhalers

The applicant proposed the use of the nebulizer supplied with the drug product in combination with a jet nebulizer-compressor (classified as a general medical device), which is different from the nebulizer used in clinical studies (PARI LC Sprint Nebulizer [PARItec] in combination with PARI BOY SX compressor [PARItec]).

The applicant's explanation about the nebulizer and compressor to be used:

The comparability of nebulization performance between the initial nebulizer/compressor combination used in clinical studies (PARI LC Sprint Nebulizer and PARI BOY SX compressor) and the proposed nebulizer/compressor combination (the nebulizer supplied with the drug product and selected

commercially available jet nebulizer compressors[7]) was evaluated by comparing [redacted],[8] an index for [redacted], and [redacted] ([redacted] see Figure 3), and [redacted] in [redacted]. Results confirmed that there are no significant differences in these parameters between the two combinations, suggesting that there is no difference in nebulization performance between the two combinations. It is acceptable to use the nebulizer supplied with the drug product in combination with any of the selected commercially available jet nebulizer compressors.

Figure 3. Comparison of [redacted] between the nebulizer used in clinical studies (PARI LC Sprint Nebulizer/PARI BOY SX; first row [redacted]) and the nebulizer supplied with the drug product, used in combination with selected commercially available jet nebulizer compressors[9]) (mean ± standard deviation [SD]).

PMDA's view:

There are no particular problems in the applicant's explanation. However, the applicant should appropriately provide healthcare professionals with information on jet nebulizer compressors to which the supplied nebulizer can be connected.

2.R.3 New excipients

The drug product contains a new excipient, tyloxapol, from the aspect of the route of administration and the concentration of the dose administered.

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7) The applicant submitted the results of studies on the combination of the nebulizer with the following 10 types of jet nebulizer compressors which are classified as general medical devices and commonly used in Japan:
PARI BOY SX, PARI Ypsita, Omron Compressor Nebulizer NE-C28, Omron Compressor Nebulizer NE-C29, Omron Compressor Nebulizer NE-C30, Millicon Cube, Millicon Pro, Voyage, InnoSpire Mini Compressor, and Soffio.

8) Calculated in accordance with [redacted] of the USP. [redacted] was calculated to obtain [redacted]. [redacted] was calculated from [redacted].

9) [redacted]. Second row, PARI BOY SX; third row, Omron Compressor Nebulizer NE-C28; fourth row, Millicon Cube; fifth row, Voyage; sixth row, InnoSpire Mini Compressor

2.R.3.1 Specifications and stability

Since tyloxapol used meets the requirements of the Japan Pharmaceutical Codex, PMDA concluded that there are no problems with the specifications and stability.

2.R.3.2 Safety

In the 3-month repeated inhalation toxicity study of tyloxapol in rats, no effect of tyloxapol was observed at 2.5 mg/mL; whereas diffuse infiltration of inflammatory cells in pulmonary alveoli, hypertrophy of alveolar epithelium, etc., were observed at ≥7.5 mg/mL; and infiltration of inflammatory cells in the perivascular area of the lung, increased cell density in the tracheal bronchus and in the paracortical area of mediastinal lymph nodes were observed at 25 mg/mL. These findings were not reversible after a 28-day recovery period.

PMDA's view:

Given that the drug product is given as a single dose, the use of tyloxapol in the drug product is acceptable. However, comparison of the concentration (7.5 mg/mL) that showed an effect on the lung in the repeated inhalation toxicity study and the concentration of tyloxapol [redacted] ([redacted] mg/mL) indicates that no sufficient safety margin is secured when the drug product is administered to humans in multiple doses by inhalation. The use of tyloxapol in the drug product should not be regarded as a valid precedent.

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

No new study data were submitted in the present application.

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

Although the present application is intended for approval of a new dosage form, no new data from non-clinical studies conducted with the primary objective of investigating pharmacokinetics were submitted because non-clinical pharmacokinetics had been evaluated for the initial application.

5. Toxicity and Outline of the Review Conducted by PMDA

Data from toxicity studies of laninamivir octanoate were submitted in support of the application for "Inavir Dry Powder Inhaler 20 mg." For the present application, a 28-day repeated inhalation toxicity study was conducted in juvenile rats. The dose of laninamivir octanoate is expressed on an anhydrous basis.

5.1 Repeated-dose toxicity

Because the inhalation suspension delivered by nebulization was likely to be easy to use for younger children with little experience of using dry powder inhalers, a 28-day repeated inhalation toxicity study was conducted in 7-day old rats, which were younger than 27-day old rats used in the previous inhalation toxicity study in juvenile rats.

Reduced body weight gain and increased inorganic phosphate in plasma were observed in the laninamivir octanoate group, but were considered to be of little toxicological significance because of the lack of any related abnormal findings. The no observed adverse effect level (NOAEL) was

determined to be 18.2 mg/kg/day (Table 3). The C_{max} and AUC_{last} of the active metabolite R-125489 on Day 28 in rats treated at 18.2 mg/kg/day were 148 ng/mL and 1730 ng·h/mL, respectively (means of values obtained in the group consisting of 3 males and 3 females). The rat exposures were compared with human exposures to the active metabolite R-125489 (C_{max} [26.6 ng/mL] and AUC_{last} [1040 ng·h/mL]), which were obtained following a single nebulized dose of laninamivir octanoate (160 mg) in healthy adult Japanese men [see Section 6.2]. The rat C_{max} was 5.6-fold the human C_{max}, and the rat AUC_{last} was 1.7-fold the human AUC_{last}. The toxicity observed in 7-day old rats did not differ from the results of toxicity studies in mature rats or 27-day old rats.

Table 3. Outline of repeated-dose toxicity study of laninamivir octanoate

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Wistar)	Inhalation	28 days (once daily) + 28-day recovery	0,[a] 2.21, 5.55, 18.2[b]	≥2.21: Reduced body weight gain, increased inorganic phosphate in plasma Reversibility: No abnormal findings	18.2	4.2.3.2-1

a) Aerosol of physiological saline solution containing [redacted] mg/mL of tyloxapol
b) The maximum inhaled dose

5.R Outline of the review conducted by PMDA

PMDA's view:

The submitted data demonstrate that laninamivir octanoate in clinical use does not pose any particular problems from a toxicological point of view.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Although the present application is intended for approval of a new dosage form, no new data on biopharmaceutic studies were submitted because the biopharmaceutics of laninamivir octanoate had been evaluated for the initial application.

Concentrations of laninamivir octanoate and its active metabolite R-125489 in plasma and in alveolar mucus and alveolar macrophages which were collected by the bronchoalveolar lavage method were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation of laninamivir octanoate and R-125489; 1.00 ng/mL in plasma, 0.100 ng/mL in alveolar mucus and alveolar macrophages).

The formulation of laninamivir octanoate inhalation suspension for nebulization used in the phase III studies (Studies J310 and J311) is the same as the proposed formulation. PARI LC Sprint Nebulizer was used (in combination with a compressor, PARI BOY SX) in the phase I study (Study CS8958-B-J109) and the phase III studies (Studies J310 and J311). For the marketing of Inavir for Inhalation Suspension, however, a single-use nebulizer connectable to a jet nebulizer compressor widely used in clinical practice is supplied with Inavir for Inhalation Suspension, with consideration given to patients' convenience and to infection control in clinical settings. It has been confirmed that there is no difference in the nebulization performance between PARI LC Sprint Nebulizer (used in

combination with a compressor, PARI BOY SX) used in clinical studies and the supplied nebulizer (used in combination with any of 10 types of jet nebulizer-compressors) [see Section 2.R.2].

6.2 Clinical pharmacology

The applicant submitted the results of pharmacokinetics (PK) studies in healthy adult Japanese men for the present application. PK parameter values are expressed as means unless specified otherwise.

Study in healthy adults (CTD 5.3.3.1-1, Study CS8958-B-J109)

A single nebulized dose of laninamivir octanoate inhalation suspension (40, 80, 160, 240, or 320 mg) was administered to healthy adult Japanese men (40 subjects included in the PK analysis). Table 4 shows the PK parameters of laninamivir octanoate and R-125489 in plasma.

Table 4. PK parameters of laninamivir octanoate and R-125489 in plasma following administration of a single nebulized dose of laninamivir octanoate inhalation suspension to healthy adult Japanese men

Dose (mg)	Number of subjects	Laninamivir octanoate				R-125489			
		C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)
40	8	40.2 ± 9.8	2.0 [1.5-3.0]	186 ± 49	1.8 ± 0.2	10.8 ± 4.3	4.0 [4.0-6.0]	257 ± 132	58.3 ± 20.7
80	8	55.9 ± 20.6	2.0 [0.5-3.0]	318 ± 144	3.1 ± 1.1	14.3 ± 4.5	6.0 [4.0-6.0]	525 ± 225	95.0 ± 42.8
160	8	77.1 ± 7.7	2.5 [2.0-3.0]	475 ± 57	4.0 ± 1.9	26.6 ± 1.62	6.0 [6.0-6.0]	1040 ± 217	115.6 ± 46.1
240	8	134.8 ± 36.2	2.0 [1.5-4.0]	1030 ± 390	34.1 ± 37.7	40.0 ± 11.8	6.0 [4.0-6.0]	1735 ± 598	144.6 ± 64.4
320	8	193.9 ± 62.0	2.5 [0.5-6.0]	1402 ± 316	55.1 ± 22.1	54.8 ± 11.8	6.0 [4.0-8.0]	2597 ± 582	165.8 ± 78.6

Mean ± SD
a) Median [range]

A single nebulized dose of laninamivir octanoate inhalation suspension (160 mg) was administered to healthy adult Japanese men (24 subjects included in the PK analysis). Table 5 shows PK parameters estimated from the concentrations of laninamivir octanoate and R-125489[10)] in plasma, alveolar mucus, and alveolar macrophages. R-125489 concentrations (mean ± standard deviation [SD]) in alveolar mucus and alveolar macrophages at 168 hours post-dose were 636.1 ± 140.2 and 277,100 ± 129,260 ng/mL, respectively.

Table 5. Estimated PK parameters of laninamivir octanoate and R-125489 following administration of a single nebulized dose of laninamivir octanoate inhalation suspension (160 mg) to healthy adult Japanese men[a)]

Biological sample	Laninamivir octanoate				R-125489			
	C_{max} (ng/mL)	t_{max} (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)
Plasma	82.5	2.00	1070	-	24.0	3.50	1180	86.5
Alveolar mucus	10,300	4.00	269,000	39.9	1460	4.00	128,000	219
Alveolar macrophages	3,860,000	24.00	238,000,000	-	480,000	24.00	52,400,000	-

-: Not calculable
a) Estimated by the model-independent analytical method using Sparse Sampling Option of WinNonlin, based on the concentrations of laninamivir octanoate and R-125489 in plasma, alveolar mucus, and alveolar macrophages.

[10)] Laninamivir octanoate and R-125489 concentrations in plasma were measured in all of the 24 subjects at 0.5, 2, and 3.5 hours post-dose and in 6 different subjects at 23.5, 71.5, and 167.5 hours post-dose. Laninamivir octanoate and R-125489 concentrations in alveolar mucus and alveolar macrophages were measured in 6 different subjects at 4, 24, 72, and 168 hours post-dose.

6.R Outline of the review conducted by PMDA

Justification for dosage regimen employed in phase III studies

The approved dose of laninamivir octanoate DPI for adult patients and pediatric patients aged ≥10 years with influenza A or B virus infection (40 mg) is different from the approved dose for pediatric patients aged <10 years (20 mg). Taking account of the fact, PMDA asked the applicant to explain the justification for selecting the administration of a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension regardless of age in the phase III studies (Studies J310 and J311) of laninamivir octanoate inhalation suspension for nebulization.

The applicant's explanation about the justification for the dosage regimen of laninamivir octanoate inhalation suspension for nebulization employed in Study J310 in adult patients and pediatric patients aged ≥10 years from a biopharmaceutical point of view:

There is a good correlation between the proportion of drug particles with particle size ≤3 or ≤5 μm and the rate of drug delivery to the respiratory organ (*J Aerosol Med Pulm Drug Deliv.* 2008;21:77-84, *J Aerosol Med.* 2006;19:522-32), which suggests that particles delivered intrapulmonarily are those with aerodynamic particle size of ≤5 μm (Basic Concepts for the Evaluation of Bioequivalence of Generic Dry Powder Inhaler [Administrative Notice dated March 11, 2016]). For the approved laninamivir octanoate DPI, FPD was defined as the amount of particles that reaches [redacted] of the cascade impactor (Andersen Cascade Impactor) (those with particle size ≤[redacted] μm) to control the inhalation characteristics, and the specification limit of FPD of laninamivir octanoate DPI 20 mg was [redacted] mg (Review Report of Inavir Dry Powder Inhaler 20 mg [dated July 7, 2010]). Since the approved dose of laninamivir octanoate DPI for adult patients and pediatric patients aged ≥10 years is 40 mg, the FPD of laninamivir octanoate DPI 40 mg is calculated to be [redacted] mg. Since the drug output from a nebulizer was correlated with the tidal volume of the patient who inhaled the drug (*Eur Respir J.* 1994;7:998-1002), the FPD of laninamivir octanoate inhalation suspension for nebulization was calculated using the nebulizer of PARItec (PARI LC Plus) and the cascade impactor (next generation impactor), with consideration given to the adult respiratory pattern[11)] obtained using a breath simulator. Results showed that FPD for the administration of laninamivir octanoate 160 mg inhalation suspension for nebulization was [redacted] mg, a value comparable to FPD ([redacted] mg) for the administration of laninamivir octanoate DPI 40 mg. These results suggest that the efficacy of laninamivir octanoate 160 mg inhalation suspension is similar to that of laninamivir octanoate DPI 40 mg.

The applicant's explanation about the justification, from the point of view of clinical pharmacology, for the dosage regimen of laninamivir octanoate inhalation suspension for nebulization employed in Study J310 in adult patients and pediatric patients aged ≥10 years:

Following administration of a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension to healthy adult men, the AUC_{last} values of laninamivir octanoate and R-125489 in plasma (475 and 1040 ng·h/mL, respectively) [see Section 6.2] were not significantly different from the AUC_{last} values of laninamivir octanoate and R-125489 in plasma after a single inhaled dose of laninamivir octanoate DPI 40 mg (988 and 1070 ng·h/mL, respectively; Review Report of Inavir Dry

11) The respiratory pattern (tidal volume, 500 mL; breathing frequency, 15 breaths/min; and inhalation to expiration time ratio, 1) of adults (≥12 years of age) defined by the US Pharmacopeia for nebulizer products (<1601> Products for Nebulization-Characterization tests) was used.

Powder Inhaler 20 mg [dated July 7, 2010]). Furthermore, following administration of a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension to healthy adult men, the AUC_{last} values of laninamivir octanoate and R-125489 in alveolar mucus (269,000 and 128,000 ng·h/mL, respectively) [see Section 6.2] exceeded the AUC_{last} values of laninamivir octanoate and R-125489 in alveolar mucus after a single inhaled dose of laninamivir octanoate DPI 40 mg (178,259 and 88,077 ng·h/mL, respectively; Review Report of Inavir Dry Powder Inhaler 20 mg [dated November 5, 2013]). These results suggested that a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension is effective in patients with influenza A or B virus infection.

The drug output from a nebulizer was correlated with the tidal volume of the patient who inhaled the drug (*Eur Respir J.* 1994;7:998-1002), and there was little change in the pulmonary functions (tidal volume and minute ventilation) between before and after infection with influenza virus in an observational study[12] (*The Japanese Journal of Thoracic Diseases.* 1964;2:211-6). On the basis of these findings, the applicant considered that the PK of laninamivir octanoate and R-125489 observed in the phase I study (Study CS8958-B-J109) of laninamivir octanoate inhalation suspension for nebulization conducted in healthy adults is extrapolatable to patients with influenza virus infection.

In an observational study[13] conducted in China, both tidal volume and minute ventilation were lower in female subjects than in male subjects (*Medicine.* 2018;97:e11904). However, when FPD following the administration of laninamivir octanoate 160 mg inhalation suspension for nebulization was evaluated by changing the respiratory parameters (tidal volume, 400 to 600 mL [reference condition, 500 mL]; breathing frequency, 12 to 18 breaths/min [reference condition, 15 breaths/min]; inhalation-respiration time ratio, 0.8 to 1.25 [reference condition, 1]) in an *in vitro* system, the observed values were within the range of FPD following the administration of laninamivir octanoate DPI 40 mg ([redacted] mg). Further, in the PPK analysis on the plasma concentrations of laninamivir octanoate and R-125489 following the administration of laninamivir octanoate DPI, sex was not identified as a covariate (Review Report of Inavir Dry Powder Inhaler 20 mg [dated July 7, 2010]). These findings suggested no significant sex difference in the PK of laninamivir octanoate and R-125489.

In an observational study on pulmonary function conducted in the US,[14] the minute ventilation in different age groups (60s, 70s, 80s, and 90s) was similar to that in subjects in their 20s (*J Gerontol.* 1974;29:393-400).In addition, in an observational study on pulmonary function conducted in China, tidal volume, breathing frequency, and minute ventilation were similar between subjects aged ≥66 years and subjects aged ≤65 years (*Medicine.* 2018;97:e11904). These findings showed no significant difference in the respiratory pattern between elderly and non-elderly subjects, suggesting that the PKs of laninamivir octanoate and R-125489 in elderly patients are unlikely to be different from those in non-elderly patients receiving Inavir for Inhalation Suspension in clinical practice.

12) Ten Japanese subjects aged ≥23 and <49 years were studied.
13) A total of 101,182 Chinese subjects aged ≥10 and <82 years were studied.
14) A total of 308 American subjects aged ≥20 and <107 years were studied.

Based on the above, the dosage regimen employed in Study J310 in adult patients and pediatric patients aged ≥10 years was "a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension."

The applicant's explanation about the justification, from a biopharmaceutical point of view, for the dosage regimen of laninamivir octanoate inhalation suspension for nebulization employed in Study J311 in pediatric patients aged <10 years:
The FPD of laninamivir octanoate inhalation suspension for nebulization was calculated using the nebulizer of PARItec (PARI LC Plus) and the cascade impactor (next generation impactor), with consideration given to the respiratory pattern[15)] of children obtained using a breath simulator. Results showed that FPD for the administration of laninamivir octanoate 160 mg inhalation suspension for nebulization was [redacted] mg, which was comparable to FPD ([redacted] mg[16)]) for the administration of laninamivir octanoate DPI 20 mg, the approved dose for pediatric patients aged <10 years. Based on the results, the efficacy of laninamivir octanoate 160 mg inhalation suspension for nebulization is expected to be comparable to that of laninamivir octanoate DPI 20 mg.

PMDA's view:
The explanation of the applicant for the dosage regimens employed in the phase III studies (Studies J310 and J311) is acceptable from the points of view of biopharmaceutics and clinical pharmacology. The efficacy and safety of a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension in adult patients, pediatric patients aged ≥10 years, and pediatric patients aged <10 years with influenza virus infection are discussed in Sections 7.R.1 and 7.R.2.

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

The applicant submitted efficacy and safety evaluation data of Inavir for Inhalation Suspension in the form of results from 2 studies. Table 6 shows the outline of main clinical studies.

Table 6. Outline of main clinical studies evaluating the efficacy and safety of Inavir for Inhalation Suspension (evaluation data)

Study identifier (phase)	Study population	Dosage regimen	No. of patients included in efficacy analysis	Main endpoints
CS8958-B-J310 (Japanese phase III)	Patients aged ≥10 years with influenza virus infection	(a) A single dose of laninamivir octanoate 160 mg inhalation suspension for nebulization (b) A single dose of placebo	(a) 268 (b) 266	Efficacy Safety
CS8958-B-J311 (Japanese phase III)	Patients aged <10 years with influenza virus infection	A single dose of laninamivir octanoate 160 mg inhalation suspension for nebulization	173	Efficacy Safety

15) The respiratory pattern (tidal volume, 155 mL; breathing frequency, 25 breaths/min; and inhalation to expiration time ratio, 0.5) of children (<12 years of age) defined by the US Pharmacopeia for nebulization products (<1601> Products for Nebulization-Characterization tests) was used.
16) Even under the conditions where the aspiration flow rate and inhalation volume in children aged <10 years were taken into consideration, the FPD of laninamivir octanoate DPI was within the specification limit ([redacted] mg per 20 mg) and similar to that observed under the reference condition.

7.1 Phase III study in adults and pediatrics aged ≥10 years (CTD 5.3.5.1-1, Study CS8958-B-J310 [[redacted] 2016 to [redacted] 2017])

A placebo-controlled, randomized, single-blind (patient-blinded) parallel-group study was conducted in adult patients and pediatric patients aged ≥10 years with influenza virus infection (target sample size, 500 subjects [250 in the laninamivir octanoate group, 250 in the placebo group]) in 75 study sites in Japan in order to investigate the efficacy and safety of Inavir for Inhalation Suspension. A single nebulized dose of laninamivir octanoate 160 mg inhalation suspension or placebo was administered via a nebulizer.[17)]

The study drug was administered to all of 534 randomized[18)] subjects (268 in the laninamivir octanoate group,[19)] 266 in the placebo group[20)]). All the subjects were included in the safety analysis set and the full analysis set (FAS), and the FAS was used for primary efficacy analysis. Study discontinuation occurred in 1 patient in the laninamivir octanoate group and in 7 patients in the placebo group. The reasons for the discontinuation were "patient's request" in 1 patient in the laninamivir octanoate group and 5 patients in the placebo group; "no return visit" in 1 patient in the placebo group; and "case where a patient was judged as ineligible for the study by the investigator or subinvestigator" in 1 patient in the placebo group.

The primary efficacy endpoint of the study was the duration of influenza symptoms (time from the end of administration to the first time point at which all of influenza symptoms[21)] [headache, myalgia or arthralgia, fatigue, chills or sweating, nasal symptoms, sore throat, and cough] recorded in the patient diary resolved or became mild, with absence of the symptoms maintained for ≥21.5 hours). Table 7 and Figure 4 show the duration of influenza symptoms. The paired comparison between the laninamivir octanoate group and the placebo group showed a statistically significant difference, demonstrating the superiority of laninamivir octanoate to placebo.

17) PARI LC Sprint Nebulizer (in combination with a compressor, PARI BOY SX) was used.
18) Stratification factors used were high-risk patients (elderly patients [≥65 years of age], concurrent illness (chronic respiratory disease, chronic cardiac disease, metabolic disease [e.g., diabetes mellitus], or renal impairment), viral type (A or B), and vaccination.
19) A nebulizer with a mouthpiece was used in 266 patients and a nebulizer with a mask in 2 patients.
20) A nebulizer with a mouthpiece was used in 265 patients and a nebulizer with a mask in 1 patient.
21) Symptoms were recorded in the patient diary according to the following 4 scales:
"None: No symptom at all. The conditions same as those before influenza virus infection."
"Mild: Mild symptoms, able to perform activities of daily living as usual."
"Moderate: Moderate symptoms, with some restrictions in activities of daily living."
"Severe: Severe symptoms, with restrictions in activities of daily living, e.g., being too ill to get out of bed and requiring medication."

Table 7. Duration of influenza symptoms (FAS)

	Laninamivir octanoate (N = 268)	Placebo (N = 266)
Median [95% CI] (hours)	55.3 [48.9, 68.8]	73.6 [67.8, 84.3]
P value[a)]	0.0024	

a) Significance level, 5% (two-sided); stratified generalized Wilcoxon test with vaccination as the stratum

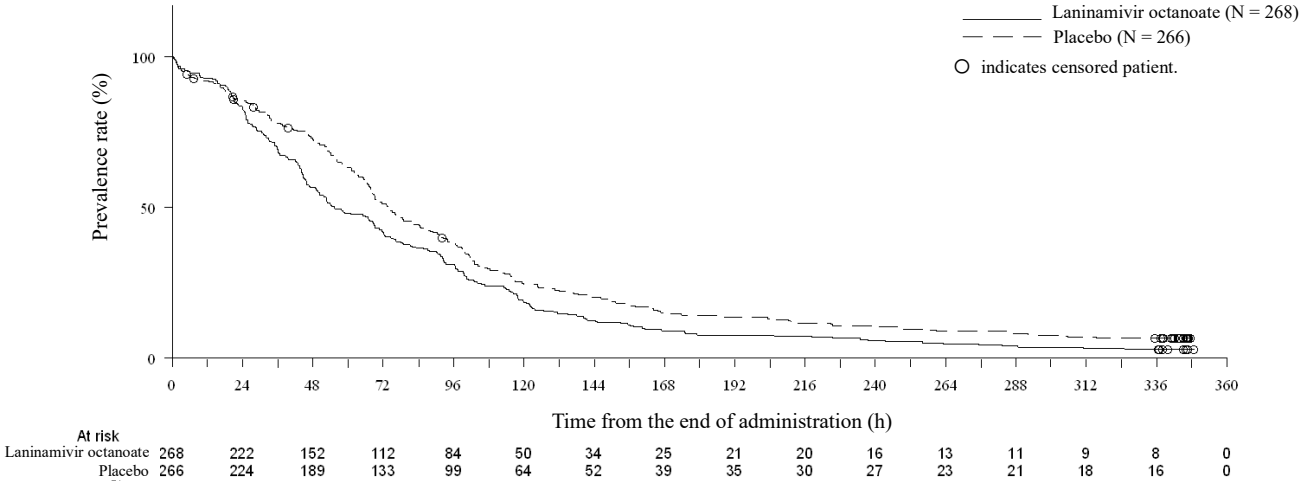

Figure 4. Kaplan-Meier estimate of duration of influenza symptoms (FAS)

Safety data were analyzed. Adverse events (including abnormal laboratory changes) were observed in 13.4% (36 of 268) of patients in the laninamivir octanoate group and in 10.5% (28 of 266) of patients in the placebo group, and adverse drug reactions[22)] were observed in 2.2% (6 of 268) of patients in the laninamivir octanoate group and in 4.1% (11 of 266) of patients in the placebo group. Table 8 shows adverse events and/or adverse drug reactions reported by ≥2 patients in either group. No death, serious adverse events, or adverse events leading to treatment discontinuations were reported.

Table 8. Adverse events and/or adverse drug reactions reported by ≥2 patients in either group (safety analysis set)

Event	Adverse events		Adverse drug reactions	
	Laninamivir octanoate (N = 268)	Placebo (N = 266)	Laninamivir octanoate (N = 268)	Placebo (N = 266)
Any event	36 (13.4)	28 (10.5)	6 (2.2)	11 (4.1)
Pharyngitis	4 (1.5)	0	0	0
Gastroenteritis	3 (1.1)	4 (1.5)	0	1 (0.4)
Diarrhoea	3 (1.1)	3 (1.1)	2 (0.7)	2 (0.8)
Nasopharyngitis	2 (0.7)	5 (1.9)	0	0
Acute sinusitis	2 (0.7)	0	0	0
Pneumonia	2 (0.7)	0	0	0
Glucose urine present	2 (0.7)	0	0	0
Headache	1 (0.4)	3 (1.1)	0	0
Dizziness	0	2 (0.8)	0	2 (0.8)
Gamma-glutamyltransferase increased	0	2 (0.8)	0	2 (0.8)
Protein urine present	0	2 (0.8)	0	2 (0.8)

n (%)

22) Adverse events considered related to the study drug.

7.2 Japanese phase III study in pediatrics aged <10 years (CTD 5.3.5.2-1, Study CS8958-B-J311 [[redacted] 2016 to [redacted] 2017])

An uncontrolled, open-label study in pediatric patients aged <10 years with influenza virus infection (target sample size, 150 subjects) was conducted in 30 study sites in Japan to investigate the efficacy and safety of Inavir for Inhalation Suspension. A single nebulized dose of laninamivir octanoate 160 mg inhalation suspension was administered via a nebulizer.[17)]

A total of 173 patients[23)] receiving the study drug were included in the safety analysis set and FAS, and the FAS was used for primary efficacy analysis. Study discontinuation occurred in 3 patients. The reasons for the discontinuation were "patient's request" in 1 patient and "adverse events calling for study discontinuation" in 2 patients.

The primary efficacy endpoint of the study was the duration of influenza symptoms (time from the end of administration to the first time point at which 2 symptoms[21)] [cough and nasal symptoms] recorded in the patient diary resolved or became mild, with a body temperature of ≤37.4°C for ≥21.5 hours). The median value (95% confidence interval [CI]) of the duration of influenza symptoms was 49.0 [43.0, 61.0] hours. Figure 5 shows the Kaplan-Meier estimate.

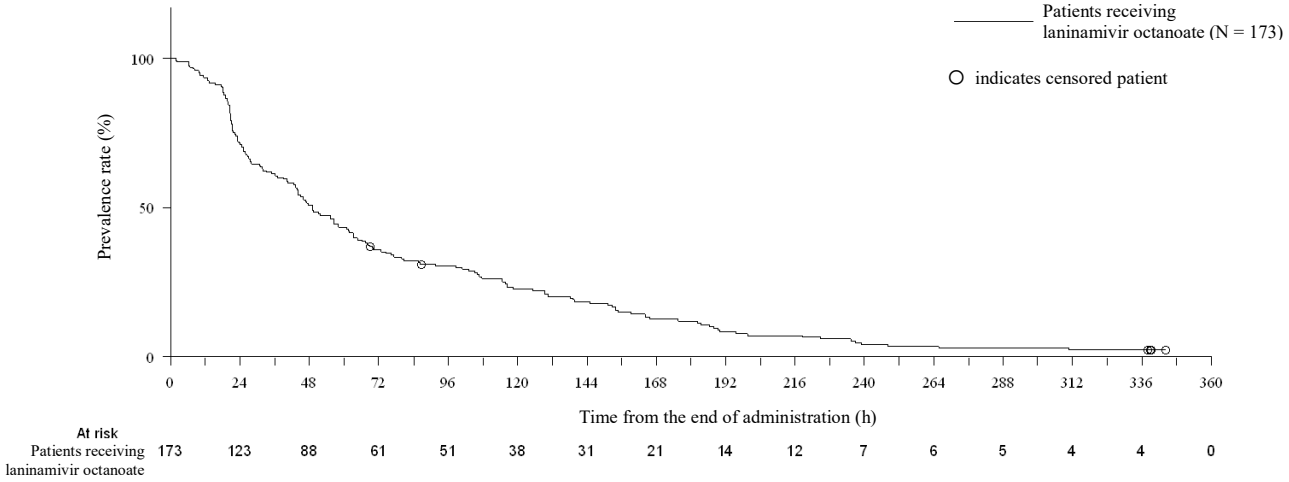

Figure 5. Kaplan Meier estimate of duration of influenza symptoms (FAS)

Safety data were analyzed. Adverse events (including abnormal laboratory changes) were observed in 20.2% (35 of 173) of patients, and adverse drug reactions[22)] were observed in 1.7% (3 of 173) of patients. Table 9 shows adverse events and/or adverse drug reactions reported by ≥2 patients.

[23)] A nebulizer with a mouthpiece was used in 82 patients and a nebulizer with a mask in 91 patients.

Table 9. Adverse events and/or adverse drug reactions reported by ≥2 patients (safety analysis population)

Event	Adverse events (N = 173)	Adverse drug reactions (N = 173)
Any event	35 (20.2)	3 (1.7)
Nasopharyngitis	7 (4.0)	0
Epistaxis	4 (2.3)	0
Mumps	3 (1.7)	0
Otitis media	2 (1.2)	0
Constipation	2 (1.2)	1 (0.6)
Vomiting	2 (1.2)	1 (0.6)

n (%)

No death or serious adverse events were observed.

Adverse events leading to treatment discontinuation were observed in 2 patients (both pharyngitis bacterial and conjunctivitis bacterial in 1 patient, nasopharyngitis in 1 patient). All adverse events were considered unrelated to the study drug, and the outcome of the events was reported as resolving or resolved.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

On the basis of the results of the following reviews, PMDA concluded that the efficacy of Inavir for Inhalation Suspension (or laninamivir octanoate inhalation suspension) is promising for the treatment of patients with influenza A or B virus infection. Because only limited information is available particularly on the efficacy of Inavir for Inhalation Suspension in pediatric patients aged <3 years, on the use of Inavir for Inhalation Suspension in patients with influenza A (H1N1) and B virus infection, and on the efficacy of laninamivir octanoate inhalation suspension delivered via the supplied mask-type nebulizer, any new information should be communicated appropriately to healthcare professionals when it becomes available.

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

7.R.1.1 Efficacy in adults and pediatrics aged ≥10 years

The applicant's explanation about the efficacy of Inavir for Inhalation Suspension in adult patients and pediatric patients aged ≥10 years with influenza virus infection:

The primary efficacy endpoint of Study J310 was the duration of influenza symptoms, and the study demonstrated the superiority of laninamivir octanoate to placebo in terms of the duration of influenza symptoms [see Section 7.1]. The median duration of influenza symptoms [95% CI] was 55.3 [48.9, 68.8] hours in the laninamivir octanoate group and 73.6 [67.8, 84.3] hours in the placebo group.

Table 10 shows the duration of influenza symptoms by age group. The between-group difference in the duration of influenza symptoms in each age group tended to be similar to that in the overall population.

Table 10. Duration of influenza symptoms in subpopulation by age group (Study J310, FAS)

Age	Treatment group	Number of patients	Median [95% CI] (hours)
≥10 and ≤18	Laninamivir octanoate	92	75.5 [46.5, 96.4]
	Placebo	66	82.5 [56.3, 96.6]
≥19 and ≤64	Laninamivir octanoate	167	52.8 [45.6, 66.9]
	Placebo	189	71.5 [66.7, 84.3]
≥65	Laninamivir octanoate	9	42.9 [1.1, 156.2]
	Placebo	11	71.1 [48.0, 165.8]

The above results demonstrate the efficacy of Inavir for Inhalation Suspension in adult patients and pediatric patients aged ≥10 years with influenza virus infection.

PMDA's view:
Study J310 demonstrated the superiority of laninamivir octanoate to placebo in terms of the duration of influenza symptoms. Therefore, the efficacy of Inavir for Inhalation Suspension is promising in adult patients and pediatric patients aged ≥10 years with influenza virus infection.

7.R.1.2 Efficacy in pediatrics aged <10 years

The applicant's explanation about the efficacy of Inavir for Inhalation Suspension in pediatric patients aged <10 years with influenza virus infection:
In Study J311, the median duration of influenza symptoms [95% CI] in patients receiving laninamivir octanoate was 49.0 [43.0, 61.0] hours, which was not significantly different from the median duration of influenza symptoms [95% CI] (55.3 [48.9, 68.8] hours) observed in the laninamivir octanoate group in Study J310 conducted in adult patients and pediatric patients aged ≥10 years.

Table 11 shows the duration of influenza symptoms by age group. The median duration of influenza symptoms tended to be longer particularly in pediatric patients aged <3 years than in other age groups, though only a limited number of patients in this age group were available for analysis. However, laninamivir octanoate inhalation suspension is considered to have a certain level of efficacy even in pediatric patients aged <3 years, taking account of the following points:

- Younger children who generally have immature immune system have a longer time to alleviation of influenza symptoms (*Pediatr Nurs.* 2009;35:335-45).

- Pediatric patients aged <3 years required frequent monitoring and caregiving by their parents or legally accepted representative. In the study, therefore, those patients were monitored more carefully for nasal symptoms and cough in particular among influenza symptoms, compared with patients in other age groups. This may have resulted in over-scoring of severity of each symptom.

- The median time [95% CI] to a body temperature ≤37.4°C was 33.1 [21.7, 45.1] hours in pediatric patients aged <3 years, 33.4 [20.0, 42.6] hours in pediatric patients aged ≥3 and <5 years, and, 27.6 [25.1, 33.1] hours in pediatric patients aged ≥5 years, showing no significant difference among age groups.

Table 11. Duration of influenza symptoms by age group (Study J311, FAS)

Age (years)	Number of patients	Median [95% CI] (hours)
<3	27	77.3 [33.1, 153.9]
≥3 and <5	44	57.2 [27.5, 105.2]
≥5	102	43.9 [31.0, 56.5]

The applicant considers that these results demonstrate the efficacy of Inavir for Inhalation Suspension in pediatric patients aged <10 years with influenza virus infection.

PMDA's view:
The efficacy of Inavir for Inhalation Suspension is promising for the treatment of pediatric patients aged <10 years with influenza virus infection, based on the following findings:

- The efficacy of laninamivir octanoate inhalation suspension for nebulization was demonstrated in Study J310 in adult patients and pediatric patients aged ≥10 years.

- In Study J310, the duration of influenza symptoms tended to be longer in pediatric patients aged ≥10 and ≤18 years than in adult patients both in the laninamivir octanoate group and the placebo group. However, no clear difference was observed in the duration of influenza symptoms between the laninamivir octanoate group in Study J310 (pediatrics ≥10 years of age) and the laninamivir octanoate group in Study J311 (pediatrics <10 years of age).

- There appeared to be no significant difference in lung exposure to laninamivir octanoate between pediatrics and adults receiving laninamivir octanoate inhalation suspension [see Section 6.R].

However, given limited experience with the use of laninamivir octanoate inhalation suspension for nebulization in pediatric patients aged <3 years and a tendency toward prolonged duration of influenza symptoms in the younger age group, post-marketing information on the efficacy of Inavir for Inhalation Suspension, particularly in pediatric patients aged <3 years, should be collected continuously, and any new information should be communicated appropriately to healthcare professionals when it becomes available.

7.R.1.3 Efficacy by type and subtype

The applicant's explanation about the efficacy of Inavir for Inhalation Suspension by influenza virus type and subtype:
Table 12 shows the duration of influenza symptoms by influenza virus type and subtype detected in Studies J310 and J311.

Table 12. Duration of influenza symptoms by influenza virus type and subtype (FAS)

	Study J310		Study J311
	Laninamivir octanoate	Placebo	Laninamivir octanoate
Influenza A (H1N1) virus			
Number of patients	1	5	4
Median [95% CI] (hours)	92.5[a)]	260.9 [71.5, -]	36.1 [20.0, 265.7]
Influenza A (H3N2) virus			
Number of patients	262	258	161
Median [95% CI] (hours)	54.7 [48.7, 68.8]	73.5 [67.0, 82.5]	47.1 [40.2, 57.8]
Influenza B virus			
Number of patients	4	3	7
Median [95% CI] (hours)	86.6 [28.7, 118.0]	73.2 [7.5, 292.1]	85.8 [20.0, 164.0]

- Not calculable
a) Individual value

Studies J310 and J311 were conducted in the 2016/2017 season, resulting in a majority of study subjects being infected with influenza A (H3N2) virus. In Study J310, the duration of influenza symptoms in patients infected with influenza A (H3N2) virus tended to be shorter in the laninamivir octanoate group than in the placebo group. The duration of influenza symptoms in the laninamivir octanoate group in Study J311 tended to be shorter than in the placebo group in Study J310.

There are limitations to the assessment of study data because only a limited number of patients infected with influenza A (H1N1) or influenza B virus were included in both Studies J310 and J311. However, the efficacy of Inavir for Inhalation Suspension is interpreted by the applicant as shown below.

Laninamivir octanoate DPI was demonstrated to be effective for the treatment of influenza A or B virus infection, and approved in September 2010 for the indication for the treatment of influenza A or B virus infection. A total of 8 clinical studies were conducted before the initial approval of laninamivir octanoate DPI (2007/2008 season and 2008/2009 season). In the studies, the geometric mean [range] of 50% inhibitory concentration (IC_{50}) of the active metabolite of laninamivir octanoate (R-125489) against neuraminidase (NA) activity of clinical isolates in the 2007/2008 and 2008/2009 seasons was 1.30 and 1.70 [0.45, 4.40] nmol/L, respectively, against influenza A (H1N1) virus and 17.23 and 18.11 [9.0, 29] nmol/L, respectively, against influenza B virus (Review Report of Inavir Dry Powder Inhaler 20 mg [dated July 7, 2010]). In the subsequent post-marketing surveillance on laninamivir octanoate DPI, the IC_{50} of the active metabolite of laninamivir octanoate (R-125489) against NA activity was measured over 7 seasons from 2010/2011 to 2016/2017. The geometric mean of IC_{50} in each season (except seasons in which influenza A (H1N1) virus or influenza B virus was not isolated or identified) ranged from 1.37 to 2.15 nmol/L against influenza A (H1N1)pdm09 virus and from 11.90 to 21.41 nmol/L against influenza B virus, showing no significant changes from the IC_{50} based on the data submitted for the initial application. The maximum IC_{50} observed in individual clinical isolates was 12.00 nmol/L (4.16 ng/mL) against influenza A (H1N1)pdm09 virus and 47.00 nmol/L (16.28 ng/mL) against influenza B virus. Clinical isolates with IC_{50} >50 nmol/L, which were considered to be resistant to the drug administered (*Antiviral Res.* 2001;49:147-56), were not detected.

The dosage regimen employed in the phase III studies of laninamivir octanoate inhalation suspension was a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension. This dose exceeds, or is comparable to, the FDP for the administration of laninamivir octanoate DPI 40 mg as the

approved dose and the exposure to laninamivir octanoate and its active metabolite (R-125489) in plasma and alveolar mucus [see Section 6.R].

Among the clinical studies so far conducted on laninamivir octanoate DPI, those enrolling a certain number of patients with influenza B virus infection showed the following results, supporting the efficacy of laninamivir octanoate DPI in patients infected with influenza B virus:

- In the phase II study (Study CS8958-A-A202) in Taiwanese patients aged ≥18 years with influenza virus infection, the median duration of influenza symptoms [95% CI] in the population of patients with influenza B virus infection (25.5% [12 of 47] of patients in the laninamivir octanoate DPI 10 mg group, 22.6% [12 of 53] of patients in the laninamivir octanoate DPI 20 mg group, 19.1% [9 of 47] of patients in the placebo group) (PPS) was 62.4 (21.8, 116.2) hours in the 10 mg group and 58.4 (21.2, 112.8) hours in the 20 mg group, which tended to be shorter than the result in the placebo group (112.8 [86.6, 296.8] hours).

- In the clinical study (Study CS8958-A-J302) in Japanese pediatric patients aged ≤9 years, the median duration of influenza symptoms [95% CI] in the population of patients with influenza B virus infection (14.8% [9 of 61] of patients in the laninamivir octanoate DPI 20 mg group, 16.4% [10 of 61] of patients in the laninamivir octanoate DPI 40 mg group, 16.1% [10 of 62] of patients in the oseltamivir phosphate group) (FAS) was 83.5 (66.6, 107.8) hours in the 20 mg group and 77.6 (51.8, 95.8) hours in the 40 mg group, which tended to be shorter than the result in the oseltamivir phosphate group (127.8 [77.1, 165.3] hours).

Based on the above, the applicant considers that Inavir for Inhalation Suspension is expected to be as effective as laninamivir octanoate DPI in patients infected with influenza A (H1N1)pdm09 or influenza B virus.

PMDA's view:
Given the results from the Japanese clinical studies (Studies J310 and J311), Inavir for Inhalation Suspension is expected to be effective in patients infected with influenza A (H3N2) virus. As for the efficacy of Inavir for Inhalation Suspension in patients infected with influenza A (H1N1) virus or influenza B virus, there are limitations to the evaluation based on data from Studies J310 and J311 because of the small number of patients investigated in those studies. Nevertheless, Inavir for Inhalation Suspension is considered to have a certain level of efficacy, based on data from non-clinical studies and clinical evidence obtained with laninamivir octanoate DPI, as explained by the applicant. Because of limited experience with the use of Inavir for Inhalation Suspension in patients infected with influenza A (H1N1) or influenza B virus, any new information on the efficacy of the product by influenza virus type and subtype should be communicated appropriately to healthcare professionals when it becomes available in the post-marketing setting.

7.R.1.4 Efficacy by the type of nebulizer used

The applicant's explanation about the efficacy by type of the nebulizer used:
In Studies J310 and J311, both the mouthpiece type and the mask type of PARI LC Sprint Nebulizer were available for use, and the investigator was allowed to select either type for each patient.

In Study J310 in adult patients and pediatric patients aged ≥10 years, the mouthpiece was selected for most of the patients, while the mask was used in 2 of 268 patients in the laninamivir octanoate group and in 1 of 266 patients in the placebo group. In the 2 patients who used the mask in the laninamivir octanoate group in Study J310, the durations of influenza symptoms were 44.7 and 22.5 hours which were both shorter than the median duration of influenza symptoms [95% CI] in the entire laninamivir octanoate group (55.3 [48.9, 68.8] hours).

Table 13 shows the number of patients who used the mouthpiece and patients who used the mask in Study J311 in pediatric patients aged <10 years, and the duration of influenza symptoms in each group. The median duration of influenza symptoms tended to be longer in patients who used the mask than in patients who used the mouthpiece, but no significant difference was observed between the two subgroups when an analysis was performed on the percentage of patients with influenza symptoms over the entire follow-up period.

Table 13. Duration of influenza symptoms, by the use of mouthpiece or mask[a] (Study J311, FAS)

	Number of patients	Median [95% CI] (hours)
Mouthpiece	82[b]	43.9 [27.4, 61.7]
Mask	91[c]	55.2 [45.1, 68.2]

a) PARI LC Sprint Nebulizer was used.
b) 12 patients aged <5 years and 70 patients aged ≥5 years
c) 59 patients aged <5 years and 32 patients aged ≥5 years

PMDA's view:
The mask was selected for use in more than half of the subjects in Study J311 conducted in pediatric patients aged <10 years. This suggests that there is a certain demand for the mask. However, the applicant should provide healthcare professionals with the following information: (i) The duration of influenza symptoms tended to be longer in patients who used the mask than in those who used the mouthpiece; and (ii) PARI LC Sprint Nebulizer was used in the clinical studies and there are no clinical experience with the use of the supplied mask-type nebulizer, albeit its nebulization performance confirmed in physicochemical studies. The applicant should also actively collect post-marketing information on the efficacy in patients receiving treatment using the supplied nebulizer.

7.R.1.5 Resistance to laninamivir octanoate

The applicant's explanation about the resistance to laninamivir octanoate:
In the specified use-results survey on laninamivir octanoate DPI, the trend of resistance to NA inhibitors was investigated by measuring the IC_{50} of the active metabolite of laninamivir octanoate (R-125489) and the control drugs (oseltamivir active metabolite, zanamivir, and peramivir) against NA activity in each season from the 2010/2011 to 2016/2017 flu seasons. Results showed that influenza A (H1N1)pdm09, influenza A (H3N2), and influenza B viruses were circulated from the 2010/2011 through 2016/2017 seasons, but influenza viruses with reduced susceptibility to the active metabolite of laninamivir octanoate were not detected in any of the seasons. The active metabolite of laninamivir octanoate retained antiviral activity against virus strains with reduced susceptibility to the active metabolite of oseltamivir.

PMDA's view:
PMDA confirmed that no mutations resistant to laninamivir octanoate have so far been detected. The applicant should appropriately inform healthcare professionals that no virus strains resistance to laninamivir octanoate were detected in clinical studies. In addition, the applicant should collect post-marketing information on the annual trend of resistance emergence by the type and subtype of influenza viruses continuously, and any new information should be communicated appropriately to healthcare professionals when it becomes available.

7.R.2 Safety

On the basis of the review presented below, PMDA concluded that the safety of a single dose of laninamivir octanoate inhalation suspension for nebulization (Inavir for Inhalation Suspension) in patients with influenza A or B virus infection is acceptable.

Because there is only limited experience with use of Inavir for Inhalation Suspension in pediatric patients aged <3 years and high-risk patients, post-marketing information on the safety of the product in these patient populations should be collected continuously and any new findings should be communicated appropriately to healthcare professionals. In the clinical studies of laninamivir octanoate, none of the patients showed abnormal behaviors that were considered related to laninamivir octanoate. However, there are reports on patients who, after receiving an approved influenza antiviral drug, showed abnormal behaviors with an unknown causal relationship to the drug, warranting caution in the use of laninamivir octanoate as is the case with drugs in the same class.

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

7.R.2.1 Outline of the safety of Inavir for Inhalation Suspension

The applicant's explanation about the safety of Inavir for Inhalation Suspension (laninamivir octanoate inhalation suspension for nebulization) in patients with influenza A or B virus infection:
Table 14 shows the summary of the safety results of Studies J310 and J311. Table 15 shows adverse events and/or adverse drug reactions[22)] reported by ≥2 patients in either group of these studies.

Table 14. Summary of safety results (safety analysis set)

	Study J310		Study J311
	Laninamivir octanoate (N = 268)	Placebo (N = 266)	Laninamivir octanoate (N = 173)
Adverse events	36 (13.4)	28 (10.5)	35 (20.2)
Adverse drug reactions	6 (2.2)	11 (4.1)	3 (1.7)
Serious adverse events	0	0	0
Adverse events leading to treatment discontinuation	0	0	2 (1.2)
Adverse events resulting in death	0	0	0

n (%)

Table 15. Adverse events and/or adverse drug reactions reported by ≥2 patients in either group (safety analysis set)

	Adverse events			Adverse drug reactions		
	Study J310		Study J311	Study J310		Study J311
	Laninamivir octanoate (N = 268)	Placebo (N = 266)	Laninamivir octanoate (N = 173)	Laninamivir octanoate (N = 268)	Placebo (N = 266)	Laninamivir octanoate (N = 173)
Nasopharyngitis	2 (0.7)	5 (1.9)	7 (4.0)	0	0	0
Pharyngitis	4 (1.5)	0	0	0	0	0
Epistaxis	0	0	4 (2.3)	0	0	0
Gastroenteritis	3 (1.1)	4 (1.5)	1 (0.6)	0	1 (0.4)	0
Diarrhoea	3 (1.1)	3 (1.1)	1 (0.6)	2 (0.7)	2 (0.8)	0
Mumps	0	0	3 (1.7)	0	0	0
Acute sinusitis	2 (0.7)	0	0	0	0	0
Pneumonia	2 (0.7)	0	0	0	0	0
Glucose urine present	2 (0.7)	0	0	0	0	0
Headache	1 (0.4)	3 (1.1)	0	0	0	0
Otitis media	0	0	2 (1.2)	0	0	0
Constipation	0	0	2 (1.2)	0	0	1 (0.6)
Vomiting	1 (0.4)	0	2 (1.2)	1 (0.4)	0	1 (0.6)
Dizziness	0	2 (0.8)	0	0	2 (0.8)	0
Gamma-glutamyltransferase increased	0	2 (0.8)	0	0	2 (0.8)	0
Protein urine present	0	2 (0.8)	0	0	2 (0.8)	0

n (%)

In Study J310, no clear difference was observed in the incidence or type of adverse events between the laninamivir octanoate group and the placebo group. The incidence and type of adverse events observed in Study J311 were not significantly different from those observed in the laninamivir octanoate group of Study J310. There were no adverse events specific to laninamivir octanoate inhalation suspension for nebulization, compared with the adverse events observed with laninamivir octanoate DPI.

PMDA's view:

The safety profile of laninamivir octanoate inhalation suspension for nebulization in Studies J310 and J311 was similar to that observed with laninamivir octanoate DPI. In light of this finding and others, there are no particular safety concerns about laninamivir octanoate inhalation suspension for nebulization. The safety of Inavir for Inhalation Suspension in different age groups and in high-risk patients is discussed below.

7.R.2.2 Safety of Inavir for Inhalation Suspension by age

The applicant's explanation about the safety of Inavir for Inhalation Suspension (laninamivir octanoate inhalation suspension for nebulization) in each age group:

Table 16 shows the summary of the safety of laninamivir octanoate inhalation suspension for nebulization in each age group. An adverse event corresponding to influenza-associated abnormal behavior was observed in 1 patient aged 1 year in Study J311, but the event was considered unrelated to the study drug.

Table 16. Summary of safety by age (safety analysis population)

	Study J310						Study J311			
	Placebo			Laninamivir octanoate			Laninamivir octanoate			
	≥10 and <20 years (N = 71)	≥20 and <65 years (N = 184)	≥65 years (N = 11)	≥10 and <20 years (N = 98)	≥20 and <65 years (N = 161)	≥65 years (N = 9)	<3 years (N = 27)	≥3 and <5 years (N = 44)	≥5 and <7 years (N = 47)	≥7 and <10 years (N = 55)
Adverse events	5 (7.0)	22 (12.0)	1 (9.1)	15 (15.3)	20 (12.4)	1 (11.1)	9 (33.3)	7 (15.9)	13 (27.7)	6 (10.9)
Adverse drug reactions	3 (4.2)	7 (3.8)	1 (9.1)	1 (1.0)	5 (3.1)	0	1 (3.7)	1 (2.3)	1 (2.1)	0
Serious adverse events	0	0	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	0	0	0	0	1 (3.7)	0	1 (2.1)	0
Adverse events resulting in death	0	0	0	0	0	0	0	0	0	0

n (%)

PMDA's view:

PMDA confirmed that there were no particular clinical concerns about the safety in any age group. In the clinical studies so far conducted, 1 patient receiving laninamivir octanoate had abnormal behavior although the event was considered unrelated to the study drug. Therefore, care should be taken to watch for abnormal behaviors as is the case with approved drugs in the same class. Furthermore, because of limited experience with the use of Inavir for Inhalation Suspension in pediatric patients aged <3 years in particular, post-marketing information on the safety of the product in this patient population should be collected continuously, and any new information should be communicated appropriately to healthcare professionals.

7.R.2.3 Safety of Inavir for Inhalation Suspension in high-risk patients

The applicant's explanation about the safety of Inavir for Inhalation Suspension (laninamivir octanoate inhalation suspension for nebulization) in high-risk patients (defined as the elderly [≥65 years of age] or patients with concurrent illness [chronic respiratory disease, chronic cardiac disease, metabolic disease (e.g., diabetes mellitus), or renal impairment]) in Studies J310 and J311:

In Study J310, adverse events were observed in 19.0% (4 of 21) of high-risk patients in the laninamivir octanoate group (gingivitis, pharyngitis, pneumonia, and diarrhoea in 1 patient each) and in 5.9% (1 of 17) of high-risk patients in the placebo group (blood lactate dehydrogenase increased and gamma-glutamyltransferase increased). There were no adverse events reported by ≥2 patients in the laninamivir octanoate group. The incidence of adverse events was higher in high-risk patients on laninamivir octanoate than in those on placebo, but comparable to that in non-high-risk patients on laninamivir octanoate (13.0% [32 of 247] of patients). The types of adverse events observed in high-risk patients on laninamivir octanoate were not significantly different from those observed in non-high-risk patients. The only adverse drug reaction observed in high-risk patients on laninamivir octanoate was diarrhoea. In patients receiving laninamivir octanoate in Study J311, adverse events were observed in 54.5% (6 of 11) of patients. There were no adverse events reported by ≥2 patients. The incidence of adverse events was higher in high-risk patients than in non-high risk patients, but there was no significant difference in the types of adverse events between the patient populations. No adverse drug reactions were observed in high-risk patients.

Thus, the safety profile of laninamivir octanoate inhalation suspension for nebulization in high-risk patients was similar to that of placebo, raising no noteworthy concerns.

PMDA's view:
On the basis of the results of Studies J310 and J311, PMDA confirmed that no events of particular concern have been so far reported in in high-risk patients receiving laninamivir octanoate inhalation suspension for nebulization in clinical studies. Inavir for Inhalation Suspension is a drug delivered by inhalation via a nebulizer, whereas airway hyperreactivity is generally enhanced by influenza virus infection, and then bronchospasm and reduced respiratory function were reported by patients treated with the approved laninamivir octanoate DPI. Care should be taken to watch for bronchospasm and reduced respiratory function in case where Inavir for Inhalation Suspension is used in patients with underlying chronic respiratory disease such as bronchial asthma and COPD. There is only limited experience with the use of Inavir for Inhalation Suspension in other high-risk patient populations, such as elderly patients (≥65 years of age) or patients with concurrent illness (chronic cardiac disease, metabolic disease [e.g., diabetes mellitus], or renal impairment). Post-marketing information should be collected, and any new information should be communicated appropriately to healthcare professionals when it becomes available.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of Inavir for Inhalation Suspension in patients with influenza A or B virus infection:
The approved laninamivir octanoate DPI is difficult to use in pediatric patients aged <5 years, patients with underlying respiratory disease (e.g., bronchial asthma, COPD) who have markedly reduced pulmonary function, and patients who are unable to understand the procedure for inhalation. Both laninamivir octanoate DPI and zanamivir hydrate DPI contain lactose hydrate as an excipient. These drugs have been reported to have induced anaphylaxis in patients with a history of hypersensitivity to dairy products. Careful consideration is required prior to the use of these drugs in such patient populations. Oseltamivir phosphate or peramivir hydrate can also be used in these patients who have difficulty in using dry powder inhaler.

Inavir for Inhalation Suspension can be delivered to the airway and other target organs by spontaneous breathing. In addition, Inavir for Inhalation Suspension that does not contain lactose hydrate can serve as a treatment option for patients with a history of hypersensitivity to dairy products.

A single-use nebulizer is supplied with Inavir for Inhalation Suspension for user's convenience and for infection control in clinical settings. Although investigators were allowed to choose either the mask-type nebulizer or the mouthpiece-type nebulizer for individual patients in clinical studies, the mask-type one was selected as a device supplied with the inhalation suspension so that it can be used in pediatric patients aged <5 years and elderly patients who have difficulty in using laninamivir octanoate DPI.

Thus, the applicant considers that Inavir for Inhalation Suspension can offer a new treatment option for patients who have difficulty in using laninamivir octanoate DPI.

PMDA's view:
Inavir for Inhalation Suspension can serve as one of the treatment options for patients who, in spite of the necessity for using influenza antiviral drug to treat influenza symptoms, have difficulty in using the approved laninamivir octanoate DPI because of age, complications such as respiratory disease, and lactose intolerance.

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

7.R.4 Indication

On the basis of the results of reviews presented in Sections 7.R.1 and 7.R.2, PMDA has concluded that the proposed indication of Inavir for Inhalation Suspension ("treatment of influenza A or B virus infection") is acceptable.

Post-marketing information on the efficacy of Inavir for Inhalation Suspension for the treatment of influenza B virus should be collected continuously, and any new information should be communicated to healthcare professionals if it becomes available.

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

7.R.5 Dosage and administration

On the basis of the results of reviews presented in Sections 7.R.1 and 7.R.2 and on the following review, PMDA has concluded that the proposed dosage and administration of Inavir for Inhalation Suspension ("The recommended dosage for both adults and pediatrics is 160 mg of laninamivir octanoate, suspended in 2 mL of Isotonic Sodium Chloride Solution [physiological saline solution], Japanese Pharmacopoeia grade, and then administered as a single dose by inhalation via a nebulizer") is acceptable.

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

7.R.5.1 Dosage and administration for adults and pediatrics aged ≥10 years

The applicant's explanation about the dosage and administration of Inavir for Inhalation Suspension in adults and pediatrics aged ≥10 years:
In Study J310 in adult patients and pediatric patients aged ≥10 years, a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension was selected from the biopharmaceutical and clinical pharmacologic points of view [see Section 6.R]. Study J310 demonstrated the superiority of laninamivir octanoate to placebo in terms of the duration of influenza symptoms, with acceptable safety. Based on the above, the administration of a single nebulized dose of laninamivir octanoate 160 mg (inhalation suspension) to adults and pediatrics aged ≥10 years is considered appropriate.

PMDA's view:
Taking account of the applicant's explanation, it is acceptable to select a single nebulized dose of laninamivir octanoate 160 mm (inhalation suspension) for use in adult patients and pediatric patients aged ≥10 years.

7.R.5.2 Dosage and administration in pediatrics aged <10 years

The applicant's explanation about the dosage regimen of Inavir for Inhalation Suspension in pediatrics aged <10 years:
In Study J311 in pediatric patients aged <10 years, a single nebulized dose of laninamivir octanoate 160 mg inhalation suspension was selected from the biopharmaceutical and clinical pharmacologic points of view [see Section 6.R]. In the Study J311, the median duration of influenza symptoms was 49.0 hours, which was similar to the result obtained in the laninamivir octanoate group of Study J310, demonstrating similar efficacy between the two studies. In addition, the safety of the treatment was considered to be within an acceptable range. Based on the above, the administration of a single nebulized dose of laninamivir octanoate 160 mg (inhalation suspension) to pediatric patients aged <10 years is considered justifiable.

PMDA's view:
Taking account of the applicant's explanation, it is acceptable to select a single nebulized dose of laninamivir octanoate 160 mg (inhalation suspension) for use in pediatric patients aged <10 years.

7.R.6 Post-marketing investigations

The applicant does not plan a post-marketing surveillance on Inavir for Inhalation Suspension based on additional pharmacovigilance activities.

PMDA asked the applicant to explain how to collect post-marketing information on the product, taking account of the fact that the re-examination period for laninamivir octanoate DPI expired on September 9, 2018.

The applicant's explanation:
According to the data from clinical studies so far conducted, Inavir for Inhalation Suspension did not pose any particular safety concerns in younger children. However, Inavir for Inhalation Suspension is expected to be prescribed in a certain number of children aged <5 years who possibly have difficulty in using laninamivir octanoate DPI. The following post-marketing surveillance is therefore planned to collect information on "safety in younger children" as the important missing information in the safety specification.

Specified use-results survey (younger children)

- Objective: To evaluate the safety and efficacy of Inavir for Inhalation Suspension in pediatric patients aged <5 years in routine clinical practice
- Sample size: 1000 patients
- Observation period: 15 days after the administration of Inavir for Inhalation Suspension
- Survey period: November 2019 to April 2020

Taking account of the applicant's explanation, PMDA has concluded that the safety in younger children should be included as important missing information in the safety specifications and a specified use-results survey focusing on younger children should be conducted as an additional pharmacovigilance activity.

Also, the applicant should collect post-marketing information on the safety in high-risk patients and on the efficacy and safety of Inavir for Inhalation Suspension delivered by inhalation via the supplied mask-type nebulizer.

In addition, a literature survey should be conducted to collect post-marketing information on the efficacy of Inavir for Inhalation Suspension for the treatment of influenza virus infection, classified by influenza type and subtype, and on the trend over years in the emergence of laninamivir octanoate-resistant clinical isolates. Any new information should be communicated appropriately to healthcare professionals if it becomes available.

Furthermore, the appropriate method for handling the supplied nebulizer (including the information on compressors to which the supplied nebulizer can be connected) should be provided to healthcare professionals.

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

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

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

The assessment is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

The assessment is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that Inavir for Inhalation Suspension has efficacy in the treatment of patients with influenza A or B virus infection, and that Inavir for Inhalation Suspension has acceptable safety in view of its benefits. Inavir for Inhalation Suspension is clinically meaningful because it offers a new treatment option for patients with influenza A or B virus infection.

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

Review Report (2)

April 3, 2019

Product Submitted for Approval

Brand Name	Inavir for Inhalation Solution 160 mg Set (name proposed at the submission of marketing application)
Non-proprietary Name	Laninamivir Octanoate Hydrate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	July 10, 2018

List of Abbreviations
See Appendix.

1. Content of the Review

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

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Review Report (1) (Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.3 Clinical positioning," "7.R.4 Indication," "7.R.5 Dosage and administration," and "7.R.6 Post-marketing investigations"). PMDA conducted an additional review of the following points raised at the Expert Discussion, and took actions as necessary.

1.1 Measures against nosocomial infection

The following comment was raised by an expert advisor:
Since Inavir for Inhalation Suspension is a drug delivered by inhalation via a nebulizer, ambient air may be contaminated by infectious particles, warranting measures to control nosocomial infection.

Since Inavir for Inhalation Suspension is administered by nebulization in medical facilities on an outpatient basis, patients receiving Inavir for Inhalation Suspension are more likely to come in contact with other patients for a longer period of time than patients who use other drugs in the same class. PMDA therefore instructed the applicant to inform healthcare professionals of the necessity of taking measures to control nosocomial infection in the clinical setting where Inavir for Inhalation Suspension is used. The applicant agreed to the instruction.

1.2 Risk management plan (draft)

The PMDA's conclusion presented in Section "7.R.6 Post-marketing investigations" of Review Report (1) was supported by the expert advisors. PMDA therefore has concluded that the risk management plan (draft) for Inavir for Inhalation Suspension should include safety and efficacy specifications presented in Table 17, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 18 and 19.

Table 17. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Bronchospasm, dyspnoea	• Abnormal behavior • Oculomucocutaneous syndrome, toxic epidermal necrolysis, erythema multiforme	• Safety in younger children
Efficacy specification		
Not applicable		

Table 18. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Specified use-results survey (in younger children)	Not applicable	• Preparation and distribution of materials for healthcare professionals • Preparation and distribution of materials for patients and their family members

Table 19. Outline of specified use-results survey (draft)

Objective	To collect information on the safety and efficacy of Inavir for Inhalation Suspension in younger children (<5 years of age)
Survey method	Central registry system
Population	Pediatric patients aged <5 years with influenza A or B virus infection receiving Inavir for Inhalation Suspension
Observation period	15 days after the administration of Inavir for Inhalation Suspension
Planned sample size	1000 patients (200 infants aged 0 to 1 year of age, 200 children aged 2 years, 300 children aged 3 years of age, 300 children aged 4 years of age)
Main survey items	Safety, efficacy, patient characteristics, use status of Inavir for Inhalation Suspension (including the type of nebulizer and compressor), concomitant medications, laboratory data

2. Other

Method of using the supplied nebulizer

According to the applicant's explanation, patients are supposed to use only the supplied mask-type nebulizer for treatment with Inavir for Inhalation Suspension. However, the investigator was allowed to select either the mask-type or the mouthpiece-type nebulizer for individual patients in clinical studies. As a result, most of the patients (266 of 268 patients in the laninamivir octanoate group and 265 of 266 patients in the placebo group) opted for the mouthpiece-type nebulizer in Study J310 in adult patients and pediatric patients aged ≥10 years. In Study J311, not a few pediatric patients aged <5 years (12 of 71 patients) also opted for the mouthpiece-type nebulizer.

PMDA asked the applicant to explain whether it is possible for patients to use the supplied nebulizer by directly holding it in their mouth at their request.

The applicant's explanation about the method of using the supplied nebulizer:
The diameter of the tube connecting the mask and the nebulizer supplied with Inavir for Inhalation Suspension is approximately 18 mm, and the circumference of the tube is not significantly different from the size of the outer part of the mouthpiece of commercially available nebulizers. It is therefore possible for patients to use the supplied nebulizer by holding the tube directly in the mouth instead of connecting to the mask.

Taking account of the applicant's explanation, PMDA instructed the applicant to inform healthcare professionals that the patients can use Inavir for Inhalation Suspension by holding in the mouth the connecting tube of the supplied nebulizer, and to improve the supplied nebulizer in the post-marketing setting, so that the nebulizer can provide better usability as the mouthpiece type. The applicant agreed to the instructions.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

4. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below with the following condition. Since the present application has been submitted for a drug with a new dosage form, the re-examination period is 4 years. The product is not classified as a biological product or a specified biological product. The drug product is not classified as a poisonous drug or a powerful drug.

Indication
Treatment of influenza A or B virus infection

Dosage and Administration

The recommended dosage for both adults and pediatrics is 160 mg of laninamivir octanoate, suspended in 2 mL of Isotonic Sodium Chloride Solution (physiological saline solution), Japanese Pharmacopoeia grade, and then administered as a single dose by inhalation via a nebulizer.

Approval Condition

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

Appendix

List of Abbreviations

AUC	Area under the plasma concentration-time curve
AUC_{last}	Area under the plasma concentration-time curve up to the last quantifiable time
C_{max}	Maximum plasma concentration
FAS	Full analysis set
FPD	Fine particle dose
IC_{50}	50% inhibitory concentration
Inavir for Inhalation Suspension	Inavir for Inhalation Suspension 160 mg Set (Inavir for Inhalation Solution 160 mg Set)
Laninamivir octanoate	Laninamivir octanoate
Laninamivir octanoate dry powder inhaler (DPI)	Inavir Dry Powder Inhaler 20 mg
Laninamivir octanoate inhalation suspension	Inhalation suspension which is a component of Inavir for Inhalation Suspension 160 mg Set (Inavir for Inhalation Solution 160 mg Set)
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
NA	Neuraminidase
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
Study J310	Study CS8958-B-J310
Study J311	Study CS8958-B-J311
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach maximum plasma concentration