Report on the Deliberation Results

November 26, 2013
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]	November 15, 2012

[Results of deliberation]
In the meeting held on November 18, 2013, the Second Committee on New Drugs concluded that the application for partial changes for 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 re-examination period is equal to the remaining period of the 8-year re-examination period determined for the product indicated for the treatment of influenza virus infection (until September 9, 2018).

**Japanese Accepted Name (modified INN)*

Review Report

November 5, 2013
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]	November 15, 2012
[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, (4) Drugs with a new indication, (6) Drugs with a new dosage
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV

Review Results

November 5, 2013

[Brand name] Inavir Dry Powder Inhaler 20 mg
[Non-proprietary name] Laninamivir Octanoate Hydrate
[Applicant] Daiichi Sankyo Company, Limited
[Date of application] November 15, 2012

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the proposed product (Inavir) in preventing influenza virus infection has been demonstrated, and its safety is acceptable in view of the observed benefits.

The prophylactic effect of Inavir against influenza B virus infection and the efficacy and safety of Inavir in populations at high risk for influenza virus infection should be further investigated in the post-marketing surveillance. Also, the development of the product for use in children aged <10 years should be expedited.

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

[Indication] Treatment <u>and prophylaxis</u> of influenza A or B virus infection
(The underlined part denotes an addition.)

[Dosage and administration]
<u>1. Therapeutic use</u>
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.

<u>2. Prophylactic use</u>
<u>Adults and children aged ≥10 years:</u>
<u>Laninamivir octanoate 20 mg is administered by inhalation once daily for 2 days.</u>
(The underlined parts denote additions.)

Review Report (1)

September 3, 2013

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] November 15, 2012
[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 and prophylaxis of influenza A or B virus infection

(The underlined part denotes an addition.)

[Proposed dosage and administration]

- Therapeutic use

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.

- Prophylactic use

Laninamivir octanoate 20 mg is administered by inhalation once daily for 2 days.

(The underlined parts denote additions.)

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.

Since this application relates to the new indication and the new dosage, "data relating to quality" and the data of pharmacokinetic studies in "non-clinical data" were not submitted.

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

Laninamivir Octanoate Hydrate (hereinafter also referred to as "laninamivir octanoate") is a compound discovered by Daiichi Sankyo Company, Limited. Laninamivir octanoate is metabolized to its active metabolite R-125489, which suppresses the growth of influenza A and B viruses by inhibiting neuraminidase (NA) of these viruses.

Inavir Dry Powder Inhaler 20 mg ("Inavir") is a dry powder inhaler containing 20.76 mg of Laninamivir Octanoate Hydrate (equivalent to 20 mg of laninamivir octanoate) and was approved for the indication for "treatment of influenza A or B virus infection" in September 2010 based on the data of clinical studies in patients with influenza A or B virus infection.

Recently, a Japanese phase III study was conducted involving family members or people living with patients with influenza A or B virus infection. The applicant claims that the efficacy and safety of laninamivir octanoate for the "prophylaxis of influenza A or B virus infection" have been demonstrated in the study, and has submitted a partial change application for Inavir.

Inavir has not been approved in foreign countries as of July 2013.

2. Data relating to quality

No new study data were submitted in this application.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

Data of an additional study were submitted as the reference data in this application.

3.(i).A.(1).1) *In vivo* anti-viral effect

(a) Anti-viral effect against influenza A virus (pre-infection administration) (Reference data 4.2.1.1-1)

BALB/c mice received a single dose of either of the following drugs 1, 4, or 7 days before nasal infection with influenza AH1-2009 virus (A/Nagasaki/I01/2009v strain)[1)]: nasal laninamivir octanoate at 0.17, 0.50, or 1.5 μmol/kg (equivalent to 0.080, 0.24, or 0.71 mg/kg, respectively), oral oseltamivir phosphate at 33 or 100 mg/kg, nasal zanamivir at 10 or 30 μmol/kg (equivalent to 3.3 or 10 mg/kg, respectively), or nasal normal saline. The number of surviving animals at 20 days after infection were counted. The results were as shown in Table 1.

Table 1. Effects of drugs administered before influenza virus infection on the survival of mice

	Survival time (days)							
Treatment group	Normal saline	Laninamivir octanoate (μmol/kg)			Oseltamivir phosphate (mg/kg)		Zanamivir (μmol/kg)	
Dose		0.17	0.50	1.5	33	100	10	30
1 day before infection	6.0 [5, 7]	>20.0* [12, >20]	>20.0* [>20]	>20.0* [>20]	8.5 [7, 15]	>20.0* [6, >20]	>20.0* [>20]	>20.0* [>20]
4 days before infection	6.5 [5, 8]	>20.0* [7, >20]	> 20.0* [16, >20]	> 20.0* [>20]	6.5 [6, 9]	7.0 [6, >20]	> 20.0* [8, >20]	> 20.0* [11, >20]
7 days before infection	6.0 [5, 10]	7.5* [6, >20]	> 20.0* [7, >20]	> 20.0* [>20]	6.0 [6, 10]	6.0 [6, 10]	8.0 [7, >20]	10.5* [7, >20]

Median [range] of 6 to 8 animals

* $P < 0.05$ (log-rank test)

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

3.(i).B.(1) Anti-viral effect of laninamivir octanoate administered before infection with influenza virus

The data submitted for this application and the data[2)] that had been previously submitted in the application for the indication for "the treatment of influenza A or B virus infection" has demonstrated the antiviral effect of laninamivir octanoate administrated to uninfected BALB/c mice (see Tables 2, 3, and 4). Based on the finding, PMDA considers that laninamivir octanoate is expected to be effective in preventing infection with influenza virus. The conclusion on the

1) IC_{50} values of R-125489, the active form of oseltamivir, and zanamivir against neuraminidase of A/Nagasaki/I01/2009v strain were 1.47, 0.555, and 1.23 nM, respectively.

2) Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.6.2.2.2.1.3-2.6.2.2.2.1.6, 2.6.2.2.2.1.11, 2.6.2.2.2.2.2, 2.6.2.2.2.5) (approved on September 10, 2010)

clinical efficacy of laninamivir octanoate is to be finalized taking account of the results of clinical studies [see "4.(iii).B.(1) Efficacy"].

Table 2. Antiviral effect of laninamivir octanoate intranasally administered 7 days before infection with influenza virus (viral titer)

Virus strain (subtype)	Treatment group	Dose (μmol/kg)	Viral titer (log_{10} [pfu/lungs])			
			1 day after infection	2 days after infection	3 days after infection	4 days after infection
A/PR/8/34(AH1)[a)]	Normal saline	-	6.67 ± 0.08	8.02 ± 0.04	7.61 ± 0.18	7.64 ± 0.02
	Laninamivir octanoate	0.18	5.70 ± 0.05	7.44 ± 0.11	7.37 ± 0.08	7.13 ± 0.07
		0.53	5.11 ± 0.13	6.93 ± 0.06	7.19 ± 0.08	7.08 ± 0.20
		1.6	4.89 ± 0.25	6.55 ± 0.14	6.95 ± 0.05	6.79 ± 0.05
A/Aichi/2/68(AH3)[b)]	Normal saline	-	5.57 ± 0.09	6.91 ± 0.06	-	-
	Laninamivir octanoate	0.48	5.05 ± 0.11	6.65 ± 0.07	-	-
		1.4	4.59 ± 0.12	6.59 ± 0.08	-	-

Mean ± standard deviation (SD) (3-5 animals)

a: Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.6.2.2.1.3)

b: Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.6.2.2.1.11)

Table 3. Antiviral effect of laninamivir octanoate intranasally administered before infection with influenza virus (survival time)

Virus strain (subtype)	Time of administration	Survival time (days)			
		Normal saline	Laninamivir octanoate (μmol/kg)		
			0.037	0.37	1.5
A/PR/8/34(AH1)[a)]	12 hours before infection	7.0 [7, 9]	12.0 [8, >20]	>20 [>20]	>20 [>20]
	1 day before infection	7.0 [7, 10]	13.0 [8, >20]	>20 [>20]	>20 [>20]
	4 days before infection	7.5 [7, 10]	8.0 [7, 16]	>20 [8, >20]	>20 [>20]
	7 days before infection	7.0 [7, 10]	8.0 [7, 9]	>20 [8, >20]	>20 [>20]

Median [range] of 8 animals

a: Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.6.2.2.1.6)

Table 4. Antiviral effect of laninamivir octanoate intranasally administered 7 days before infection with influenza virus (survival time)

Virus strain	Survival time (days)			
	Normal saline	Laninamivir octanoate (μmol/kg)		
		0.16	0.49	1.5
B/Hong Kong/5/72[a)]	8.0 [5, 12]	12.0 [7, >20]	>20 [12, >20]	>20 [9, >20]

Median [range] of 11 animals

a: Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.6.2.2.2.2)

3.(i).B.(2) Sensitivity of clinically isolated recent influenza virus strains to laninamivir octanoate

PMDA asked the applicant to explain any possible changes in the sensitivity of recent epidemic influenza virus strains to laninamivir octanoate (or its active metabolite R-125489).

The applicant explained as follows:

Table 5 shows the *in vitro* antiviral effects (neuraminidase-inhibiting activity) of R-125489 and the similar drugs against clinical isolates obtained during the 2010/2011 and 2011/2012 seasons and at approval for the current indication. The clinical isolates in the 2010/2011 and 2011/2012 seasons did not show to have decreased sensitivity to R-125489 in the comparison with the data submitted for application for laninamivir octanoate indicated for "the treatment of influenza A or B virus infection."

Table 5. Sensitivity of clinically isolated influenza virus strains to various drugs

Virus type/subtype	Year (season) isolated	No. of strains	IC_{50} (nM)			
			R-125489	Active form of oseltamivir	Zanamivir	Peramivir
Type AH1	2002-2006[a)]	8	1.29-2.63	0.658-1.86	0.751-1.68	-
	2010/2011	185	0.23-4.60	0.20-840.00	0.24-2.10	0.03-24.00
	2011/2012	0	-	-	-	-
Type AH3	2002-2006[a)]	7	7.09-14.2	0.706-1.09	3.42-7.58	-
	2010/2011	54	1.40-6.90	0.26-2.20	0.76-2.50	0.27-1.20
	2011/2012	283	1.20-7.50	0.25-2.10	0.63-4.50	0.29-1.70
Type B	2002-2006[a)]	18	10.4-26.5	3.09-13.7	3.55-7.59	-
	2010/2011	30	11.00-47.00	19.00-65.00	5.60-24.00	2.30-8.70
	2011/2012	42	7.70-26.0	6.10-27.00	3.60-11.00	1.60-5.50

a: Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.6.2.1.1.1.2)

PMDA accepted the applicant's explanation and considers that clinical isolates have not shown decreased sensitivity to laninamivir octanoate until now.

3.(ii) Summary of pharmacokinetic studies

No new study data were submitted in this application.

3.(iii) Summary of toxicology studies

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

For this application, laninamivir octanoate was assumed to be administered multiple times in clinical practice for the purpose of the prophylaxis of influenza virus infection, and a 3-month intermittent inhalation toxicity study was conducted in rats. In the data submitted in the application for the indication of "the treatment of influenza A or B virus infection," the result of inhalation toxicity study up to 4 weeks produced no toxicological findings suggestive of inter-species difference between rodents (rats) and non-rodents (dogs). Therefore, only rats were used in the intermittent inhalation toxicity study.

3.(iii).A.(1) Repeat-dose toxicity

The result of the 3-month intermittent inhalation study in rats was submitted as a repeat-dose toxicity study of laninamivir octanoate. The comparison between the no observed adverse effect level (NOAEL) in the toxicity study and the exposure[3)] to the active metabolite R-125489 in Japanese healthy male adults who received a single dose inhalation of 20 mg laninamivir octanoate (Study CS8958-A-J102)[4)] showed safety margins of approximately 68- to 83-fold in C_{max} and approximately 29- to 37-fold in AUC.

3.(iii).A.(1).1) Three-month intermittent inhalation toxicity study in rats (4.2.3.2-1)

The aerosol form was produced from Laninamivir Octanoate Hydrate powder and was administered by inhalation to male and female RccHan^{TM}:WIST rats (n = 10/sex/group) at a dose of 0 [air], 22, 42, or 76 mg/kg/dose[5)] twice weekly intermittently for 3 months. In the 22 mg/kg/dose group, 1 of 10 animals died after administration on Day 88, presumably due to an inappropriate restraining during inhalation. A hematology test showed prolonged prothrombin time in the ≥42 mg/kg/dose groups, and diffuse hypertrophy of adrenocortical fasciculata cells was observed in 1 each of males and females in the 76 mg/kg/dose group. All of these changes were within the range of the historical data, suggesting little toxicological significance.

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3) The maximum plasma concentration (C_{max}) on Day 88 and the area under the plasma concentration-time curve up to 23 hours after treatment start (AUC_{0-23h}) were used as the parameters for the exposure level in the toxicity study, and C_{max} and AUC_{0-24h} on Day 1 were used as the parameters for the exposure level in the clinical study.

4) Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.7.2.2.2.1.1.1) (approved on September 10, 2010)

5) Dose estimated from the concentration of laninamivir octanoate in the aerosol, duration of inhalation, minute ventilation, and body weight.

Based on these findings, the NOAEL was determined to be 76 mg/kg/dose, which is the maximum feasible dose.

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

PMDA considers that the submitted data do not indicate any particular problems in the toxicological aspect.

4. Clinical data

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

No new study data were submitted in the present application.

In Study J108, concentrations of laninamivir octanoate and the active metabolite R-125489 in plasma and those in alveolar epithelial lining fluid and alveolar macrophages collected by bronchoalveolar lavage (BAL) method were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS)[6].

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data for this application, the result of a single dose inhalation study (Study J108), in which the pharmacokinetics in the target tissue was evaluated following a single dose inhalation of laninamivir octanoate in Japanese healthy adult men, was submitted.

4.(ii).A.(1) Single dose inhalation study in Japanese healthy adult subjects (5.3.3.1-1, Study J108 [March 2011 to May 2011])

A total of 35 Japanese healthy adult men received a single dose inhalation of laninamivir octanoate 40 mg, and the concentrations of laninamivir octanoate and R-125489 in plasma and in bronchoalveolar lavage fluid were measured[7] to investigate the pharmacokinetics of the drug in alveolar epithelial lining fluid and in alveolar macrophages. The results were as shown in Table 6. In the alveolar epithelial lining fluid and in the alveolar macrophages 240 hours after administration, the concentrations (mean ± standard deviation [SD]) of laninamivir octanoate were 22.2 ± 14.7 ng/mL and 21,810 ± 10,021 ng/mL, respectively, and the concentrations of R-125489 were 194.4 ± 87.7 ng/mL and 34,560 ± 17,702 ng/mL, respectively.

Table 6. Pharmacokinetic parameters of laninamivir octanoate and R-125489

		C_{max} (ng/mL)	t_{max} (h)	AUC_{last} (ng·h/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
Laninamivir octanoate	Plasma	161.98	0.3	704.86	706.03	2.6
	Alveolar epithelial lining fluid	24,881.56	4.0	178,259.25	179,646.18	43.2
	Alveolar macrophages	1,282,326.57	8.0	40,659,772.46	43,673,191.43	95.8
R-125489	Plasma	25.45	3.5	825.98	841.14	45.7
	Alveolar epithelial lining fluid	3506.12	4.0	88,076.57	188,628.43	358.5
	Alveolar macrophages	143,314.88	8.0	11,220,201.04	21,742,633.06	211.0

C_{max}: Maximum concentration, t_{max}: Time to maximum concentration, AUC_{last}: Area under the concentration-time curve (AUC) up to the last quantifiable time point, $AUC_{0\text{-}inf}$: AUC up to infinity, $t_{1/2}$: Terminal phase elimination half-life
Each pharmacokinetic parameter was estimated by a model-independent analysis using Sparse Sampling Option (WinNolin), based on the concentrations in the plasma, alveolar epithelial lining fluid, and alveolar macrophages.

6) Quantitation limit: Plasma concentration, 1 ng/mL; concentration in alveolar epithelial lining fluid and in alveolar macrophages, 0.1 ng/mL

7) Bronchoalveolar lavage (BAL) was performed in 5 different subjects at each time point of 4, 8, 24, 48, 72, 168, and 240 hours after administration, and laninamivir octanoate concentrations in the plasma and in the lavage fluid were measured.

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

PMDA confirmed that the concentrations of laninamivir octanoate and R-125489 in alveolar epithelial lining fluid and in alveolar macrophages after a single dose inhalation of laninamivir octanoate 40 mg were higher than IC_{50} (50% inhibitory concentration, 0.23-47.0 nM [0.08-16.3 ng/mL]) against neuraminidase activity of influenza A and B virus up to 240 hours after administration.

Appropriateness of the proposed dosage and administration in prophylactic use is discussed in "4.(iii).B.(1).1).(a) Dosage and administration."

4.(iii) Summary of clinical efficacy and safety

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

As efficacy- and safety-related evaluation data, results of 2 Japanese phase III studies (Study J306, Study J307) were submitted in this application. Also, the result of a Japanese clinical pharmacology study (Study J108) was submitted as safety evaluation data. Table 7 lists the clinical studies submitted.

Table 7. List of clinical studies

Study name	Subjects	No. of subjects enrolled [a)]	Dosage and Administration
Study J108	Healthy adult male subjects	36	40 mg single dose inhalation
Study J306	Family members or others living with patients with influenza A or B virus infection	610	Inhalation of laninamivir octanoate (20 mg, 40 mg) or placebo once a week, 2 doses in total,
Study J307	Family members or others living with patients with influenza A or B virus infection	1711	Inhalation of laninamivir octanoate 20 mg once daily for 2 days, laninamivir octanoate 20 mg once daily for 3 days, or placebo once daily for 3 days

a) The number in Studies J306 and J307 indicates the number of randomized subjects.

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

4.(iii).A.(1).1) Single dose inhalation study in Japanese healthy adults (5.3.3.1-1, Study J108 [March 2011 to May 2011])

An open-label, uncontrolled study was conducted at a single center in Japan to investigate the pharmacokinetics in the alveoli following a single dose inhalation of laninamivir octanoate 40 mg in Japanese healthy adult men (target sample size, 35) [for pharmacokinetics, see "4.(ii) Summary of clinical pharmacology studies"].

A single dose of laninamivir octanoate 40 mg was to be administered by inhalation.

All of the 36 treated subjects were included in the safety analysis set.

The safety analysis revealed that adverse events were observed in 72.2% (26 of 36 subjects). Of these, 61.1% (22 of 36 subjects) were considered to be due to BAL that was performed to measure drug concentrations in alveolar epithelial lining fluid and in alveolar macrophages, and 19.4% (7 of 36 subjects) were not BAL-induced events. Adverse events reported by ≥2 subjects were C-reactive protein (CRP) increased in 21 subjects (BAL-induced in 20 subjects), white blood cell count increased in 10 subjects (BAL-induced in all subjects), neutrophil percentage increased in 8 subjects (BAL-induced in all subjects), lymphocyte percentage decreased in 5 subjects (BAL-induced in all subjects), and blood creatine phosphokinase increased in 2 subjects (BAL-induced in both). A causal relationship with laninamivir octanoate was ruled out for all the adverse events observed.

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

discontinuation.

4.(iii).A.(2) Phase III studies

4.(iii).A.(2).1) Japanese phase III study in family members or others living with patients with influenza A or B virus infection (5.3.5.1-1, Study J306 [20 to 20])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at 47 centers in Japan to investigate the efficacy and safety of laninamivir octanoate in prophylactic use against influenza virus infection in family members or others[8)] living with an index case patient[9)] with influenza A or B virus infection (target sample size, 600 [200 subjects per group]).

Laninamivir octanoate (20 mg, 40 mg) or placebo was to be administered by inhalation once a week, 2 doses in total.[10)]

All of the 610 randomized subjects (207 subjects in the laninamivir octanoate 20 mg group, 205 subjects in the laninamivir octanoate 40 mg group, 198 subjects in the placebo group) were included in the full analysis set (FAS), and the FAS was used for the safety analysis and the efficacy analysis.

The primary efficacy endpoint of the incidence of laboratory-confirmed influenza virus infection[11)] in the FAS was as shown in Table 8. The pairwise comparison of the incidences between the laninamivir octanoate 20 mg or the laninamivir octanoate 40 mg group and the placebo group showed no statistically significant difference ($P = 0.1633$ [laninamivir octanoate 20 mg group], $P = 0.1643$ [laninamivir octanoate 40 mg group], Fisher's exact test, multiplicity of test adjusted by Holm's method).

Table 8. Incidence of laboratory-confirmed influenza virus infection by treatment group (FAS)

Treatment group	No. of subjects	No. of infected subjects (%)	*P* value[a)]	Rate of decrease in relative risk[b)] (%)
Laninamivir octanoate 20 mg group	207	10 (4.8)	0.1633	43.7
Laninamivir octanoate 40 mg group	205	10 (4.9)	0.1643	43.2
Placebo group	198	17 (8.6)	-	-

a) Fisher's exact test using the placebo group as the control
b) 100 × (1 - incidence in the laninamivir octanoate group / incidence in the placebo group)

Figure 1 shows changes in the cumulative number of subjects with laboratory-confirmed influenza virus infection.

8) Inclusion criteria were as follows: a family member or other living with an index case patient with influenza, (b) tested negative with an influenza virus test kit, (c) body temperature (axillary) ≤36.9°C at the time of consent, (d) no symptoms indistinguishable from those of influenza at the time of consent (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough), (e) capable of inhaling the drug using the dedicated inhaler.

9) Patients who tested positive with an influenza virus kit and do not live with a family member or other who was infected with influenza A or B virus within 4 weeks before consent.

10) The first dose of study drug was to be administered on Day 1, and the second dose on Day 8.

11) The onset of laboratory-confirmed influenza virus infection was defined as the development of ≥2 of the 7 influenza symptoms (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough) in a patient who tested positive for virus PCR with body temperature ≥37.5°C. The observation period to confirm the onset of influenza virus infection was up to Day 11 where the day of the first dose of the study drug was defined as Day 1.

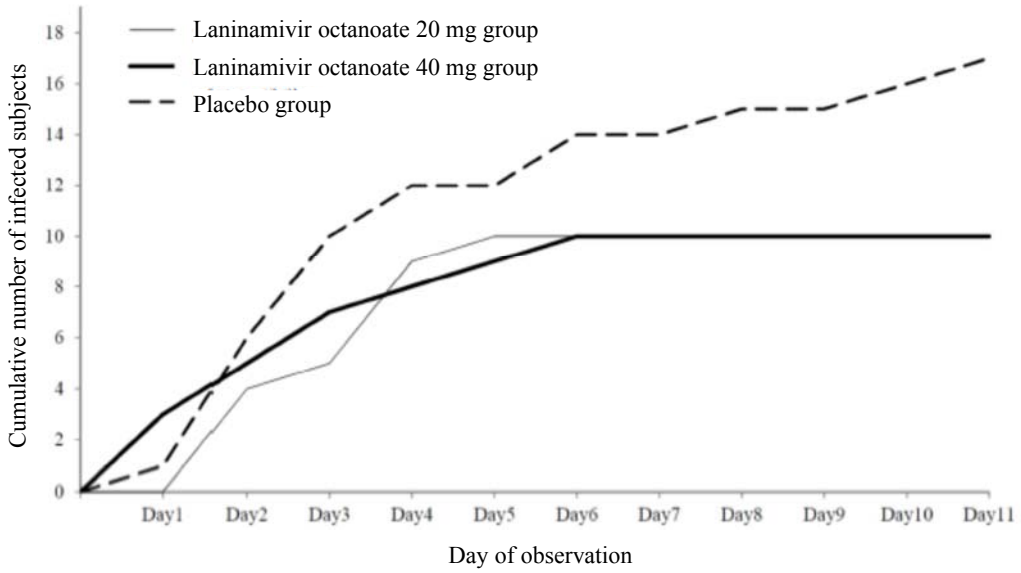

Figure 1.Changes in the cumulative number of subjects with laboratory-confirmed influenza virus infection

The safety analysis revealed that adverse events were observed in 13.5% (28 of 207 subjects) in the laninamivir octanoate 20 mg group, 14.1% (29 of 205 subjects) in the laninamivir octanoate 40 mg group, and 15.2% (30 of 198 subjects) in the placebo group. Adverse drug reactions[12)] were observed in 3.9% (8 of 207 subjects) in the laninamivir octanoate 20 mg group, 3.9% (8 of 205 subjects) in the laninamivir octanoate 40 mg group, and 2.0% (4 of 198 subjects) in the placebo group. Adverse events and adverse drug reactions with an incidence of ≥1% in any group were as shown in Table 9.

Table 9. Adverse events and adverse drug reactions with an incidence of ≥1% in any group

	Adverse events			Adverse drug reactions		
	Laninamivir octanoate 20 mg group	Laninamivir octanoate 40 mg group	Placebo group	Laninamivir octanoate 20 mg group	Laninamivir octanoate 40 mg group	Placebo group
No. of subjects evaluated	207	205	198	207	205	198
No. of subjects with the event	28 (13.5)	29 (14.1)	30 (15.2)	8 (3.9)	8 (3.9)	4 (2.0)
Diarrhoea	4 (1.9)	2 (1.0)	2 (1.0)	4 (1.9)	1 (0.5)	2 (1.0)
Pyrexia	2 (1.0)	3 (1.5)	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)
Nasopharyngitis	7 (3.4)	10 (4.9)	14 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase (ALT) increased	1 (0.5)	2 (1.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Aspartate aminotransferase (AST) increased	1 (0.5)	2 (1.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
CRP increased	1 (0.5)	3 (1.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Headache	2 (1.0)	4 (2.0)	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)
Rhinitis allergic	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhoea	0 (0.0)	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract inflammation	3 (1.4)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Number of subjects with event (%)
MedDRA/J ver.12.1

[12)] Adverse events considered by the investigator or sub-investigator as related to the study drug

There were neither deaths nor other serious adverse events.

An adverse event leading to treatment discontinuation was reported in 1 subject in the laninamivir 20 mg group (diarrhoea). A causal relationship to the study drug could not be ruled out.

4.(iii).A.(2).2) Japanese phase III study in family members or others living with patients with influenza A or B virus infection (5.3.5.1-2, Study J307 [November 2011 to April 2012])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at 80 centers in Japan to investigate the efficacy and the safety of laninamivir octanoate in prophylactic use against influenza virus infection in family members or others[13] living with an index case patient[14] with influenza A or B virus infection (target sample size, 1500 [500 subjects per group]).

In the laninamivir octanoate 20 mg × 2 group, subjects received laninamivir octanoate 20 mg or placebo by inhalation once daily for 3 days (laninamivir octanoate 20 mg on Days 1 and 2, placebo on Day 3). In the laninamivir octanoate 20 mg × 3 group, subjects received 20 mg by inhalation once daily for 3 days. In the placebo group, placebo was inhaled once daily for 3 days.

Of 1711 randomized subjects (568 subjects in the 20 mg × 2 group, 567 subjects in the 20 mg × 3 group, 576 subjects in the placebo group), 1658 subjects (550 subjects in the 20 mg × 2 group, 550 subjects in the 20 mg × 3 group, 558 subjects in the placebo group) were included in the FAS, excluding 53 subjects (4 subjects with GCP violation,[15] 3 subjects untreated with the study drug, 6 subjects without observation data necessary for the judgment of influenza virus infection, 40 subjects in a medical institution that discontinued the study due to difficulty in the proper conduct of the clinical study[16]). Of those in the FAS, 1451 subjects (487 subjects in the 20 mg × 2 group, 486 subjects in the 20 mg × 3 group, 478 subjects in the placebo group) were determined to be FAS index infected virus negative at baseline (FASIINAB) and the FASIINAB was used for the efficacy analysis, excluding 30 subjects living with an index case patient with influenza virus infection who tested negative by PCR test at enrollment and 177 subjects who did not test negative by PCR test at enrollment. Of 1711 randomized subjects, 1664 subjects (552 subjects in the 20 mg × 2 group, 553 subjects in the 20 mg × 3 group, 559 subjects in the placebo group) were included in the safety analysis set, excluding 47 subjects (4 subjects with GCP violation, 3 subjects untreated with the study drug, 40 subjects in the medical institution that discontinued the study due to difficulty in the proper conduct of the clinical study).

The primary efficacy endpoint of the incidence of laboratory-conirmed influenza virus infection[11] in the FASIINAB was as shown in Table 10. A statistically significant difference in the incidence was observed in the pairwise comparison between each laninamivir octanoate group and the placebo group ($P < 0.001$ in each laninamivir octanoate group, Fisher's exact test. The multiplicity of the test was adjusted by the Hochberg method).

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13) Inclusion criteria were as follows: (a) a family member or any person living with an index case patient with influenza virus infection who was able to provide consent on the same day that the said patient provided consent, (b) was confirmed by the investigator or sub-investigator not to have been infected with an influenza virus, (c) with body temperature (axillary) ≤36.9°C at the time of consent, (d) had no symptoms indistinguishable from influenza symptoms at the time of consent, (e) was ≥10 years of age at the time of consent.

14) Patients who tested positive with the influenza virus test kit and were the first to be infected by influenza A or B virus since [redacted] 20[redacted] among their family members or others living together.

15) Two subjects were excluded due to inappropriate changes made to their subject diaries, and 2 subjects due to the missing consent date on the consent form of the index case patient with influenza virus infection living together.

16) The medical institution was found to have made inappropriate changes to the subject diaries of 2 subjects, which was considered as GCP violation, and the rest of 40 other subjects enrolled in the study at the institution were also excluded at the discretion of the sponsor because of lack of data integrity.

Table 10. Incidence of laboratory-confirmed influenza virus infection by treatment group (FASIINAB)

Treatment group	No. of subjects	No. of infected subjects (%)	*P* value[a)]	Rate of decrease in relative risk[b)] (%)
Laninamivir octanoate 20 mg × 2 group	487	19 (3.9)	<0.0001	77.0
Laninamivir octanoate 20 mg × 3 group	486	18 (3.7)	<0.0001	78.1
Placebo group	478	81 (16.9)	-	-

a) Fisher's exact test using the placebo group as the control
b) 100 × (1 – incidence in the laninamivir octanoate group / incidence in the placebo group)

Figure 2 shows changes in the cumulative number of subjects with laboratory-confirmed influenza virus infection.

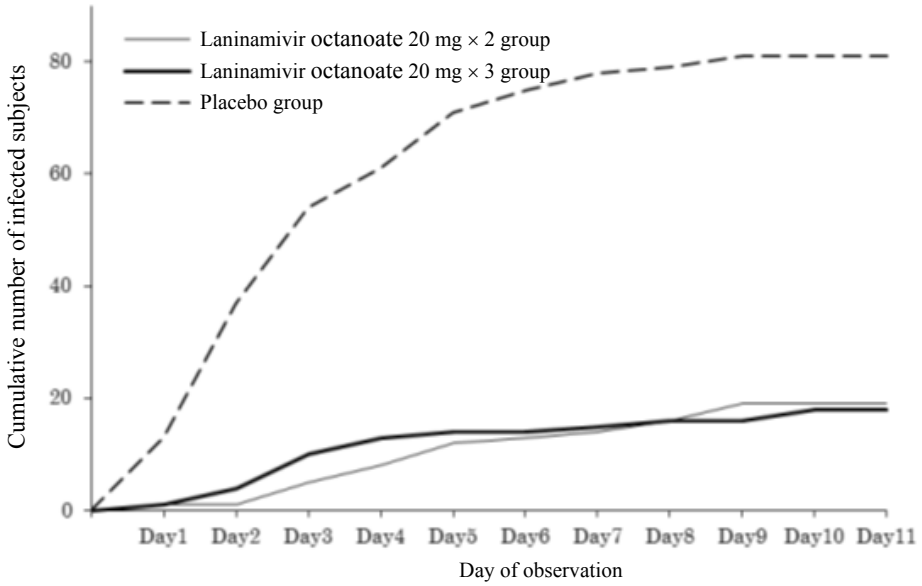

Figure 2. Changes in the cumulative number of subjects with laboratory-confirmed influenza virus infection (FASIINAB)

The safety analysis revealed that adverse events were observed in 13.4% (74 of 552 subjects) in the 20 mg × 2 group, 13.0% (72 of 553 subjects) in the 20 mg × 3 group, and 11.6% (65 of 559 subjects) in the placebo group. Adverse drug reactions[12)] were observed in 3.1% (17 of 552 subjects) in the 20 mg × 2 group, 4.7% (26 of 553 subjects) in the 20 mg × 3 group, and 2.7% (15 of 559 subjects) in the placebo group. Adverse events and adverse drug reactions with an incidence of ≥1% in any group were as shown in Table 11.

Table 11. Adverse events and adverse drug reactions with an incidence of ≥1% in any group

	Adverse events			Adverse drug reactions		
	Laninamivir octanoate 20 mg × 2 group	Laninamivir octanoate 20 mg × 3 group	Placebo group	Laninamivir octanoate 20 mg × 2 group	Laninamivir octanoate 20 mg × 3 group	Placebo group
No. of subjects evaluated	552	553	559	552	553	559
No. of subjects with event	74 (13.4)	72 (13.0)	65 (11.6)	17 (3.1)	26 (4.7)	15 (2.7)
Diarrhoea	5 (0.9)	1 (0.2)	6 (1.1)	4 (0.7)	1 (0.2)	4 (0.7)
Nasopharyngitis	12 (2.2)	18 (3.3)	14 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	7 (1.3)	6 (1.1)	2 (0.4)	3 (0.5)	3 (0.5)	0 (0.0)
Upper respiratory tract inflammation	11 (2.0)	7 (1.3)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)

Number of subjects with event (%)
MedDRA/J ver.15.0

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

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

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

As a result of the following review mainly on the results of Study J307 submitted, PMDA concluded that laninamivir octanoate is effective in preventing influenza A or B virus infection.

4.(iii).B.(1).1) Design of Study J307

(a) Dosage and administration

PMDA asked the applicant to explain the justification for the dosage and administration used in Studies J306 and J307.

The applicant explained as follows:
Antiviral drugs for influenza are expected to prevent infection when administered prior to the onset of symptoms. The residue of the drug in the trachea and the lungs exhibits an inhibitory effect on the growth of influenza virus invading into the organs. Given the logarithmic increase of influenza virus, the prophylactic regimen is such a low dose that it is adequate for sub-peak viral load, or is lower than the therapeutic dose. Therefore, based on the results of the global phase III study (Study J301),[17] etc. of laninamivir octanoate conducted for the treatment of influenza virus infection, the dose of 20 mg, which was used in a low dose group and shown to be non-inferior to oseltamivir phosphate, was used in Study J306 in addition to the dose of 40 mg, which is the optimal clinical dose in therapeutic use.

Considering the duration of influenza virus shedding in index case patients with influenza virus infection and the latent period of the virus in subjects, etc., the prophylactic effect of the drug should persist for ≥10 days in contacts of patients. According to the result of the clinical pharmacology study of laninamivir octanoate (Study J107, a PK study using the inhaler for commercial use),[18] the drug exposure (C_{max}) on Day 7 after a single-dose administration of laninamivir octanoate 20 mg or 40 mg was approximately 1/15 times that 4 hours after administration, around which the peak viral load is reached in therapeutic use, and approximately 1/4 times that 24 hours after administration. The result indicated the prophylactic effect of the drug is maintained until 7 days after administration. Therefore, in Study J306, the drug was planned to be administered 2 times at a 7-day interval for the convenience in clinical practice, in

[17] Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.7.6.10.5.2.3) (approved on September 10, 2010)
[18] Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.7.6.3) (approved on September 10, 2010)

expectation of prophylactic effect lasting for 10 days.

According to published reports of clinical studies on post-contact prophylaxis of influenza virus infection by the similar drugs (oseltamivir phosphate, zanamivir hydrate),[19),20),21),22)] the reduction rates of relative risks were 72% to 92%. In the past 10 seasons (2001/02 through 2010/11), the reduction rates of relative risks by vaccination[23)] were 20.5% to 78.6% for type A virus and were 0.0% to 64.8% for type B virus. In the 2009/2010 season when the epidemic virus type matched with the vaccine type, the reduction rate of relative risks was 69.7%. Taking account of the findings, a clinically significant reduction rate of relative risks should be ≥70%. Therefore, in Study J306, the reduction rate of relative risks in each laninamivir octanoate group against the placebo group was hypothesized to be 70%, based on the assumption that the incidence of laboratory-confirmed influenza virus infection in the placebo group would be approximately 10.0%. However, in this study, the primary endpoint of the incidence of laboratory-confirmed influenza virus infection was 8.6% (17 of 198 subjects)[24] in the placebo group, while it was 4.8% (10 of 207 subjects) in the laninamivir octanoate 20 mg group and 4.9% (10 of 205 subjects) in the laninamivir octanoate 40 mg group, failing to demonstrate the superiority of laninamivir octanoate to placebo. Although prophylactic effect of laninamivir octanoate on influenza virus infection was suggested following once-weekly administration of 20 mg or 40 mg as compared with the placebo, it was considered not clinically sufficient.

A cause of the failure to demonstrate an adequate prophylactic effect in Study J306 was examined from the aspect of the pharmacokinetics of laninamivir octanoate. The result of Study J108 showed that, following a single dose inhalation of laninamivir octanoate 40 mg, R-125489 concentrations in alveolar epithelial lining fluid and in alveolar macrophages remained above the IC_{50} value for an extended period [see "4.(ii).B. Outline of the review by PMDA"]. By the BAL method used in this examination, usually samples such as cell components and non-cellular components (liquid components) are collected from the alveolar region and the peripheral airways. However, influenza virus infection involves not only these organs but also the upper airway including the pharynx and larynx and the lower airways including the trachea and the main bronchi, in which pharmacokinetics of laninamivir octanoate was not investigated in Study J108. Although the absence of data on the pharmacokinetics of the drug in these organs precluded the presentation of clear evidence, the result of Study J306 may have suggested that the elimination of the drug was promoted in these organs by ciliary motion and food/drink intake as compared to the alveolar region.

The failure to demonstrate a prophylactic effect in Study J306 was investigated from a clinical aspect as well. In the global phase III study (Study J301) that investigated the efficacy and safety of laninamivir octanoate in the treatment of patients with influenza virus infection, virus titers and the percentage of patients who had virus shedding after infection tended to increase for several

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19) Welliver R et al. *JAMA*. 2001;285(6):748-754
20) Hayden FG et al. *J Infect Dis*. 2004;189(3):440-449
21) Hayden FG et al. *N Engl J Med*. 2000;343(18):1282-1289
22) Monto AS et al. *J Infect Dis*. 2002;186(11):1582-1588
23) Influenza study group, Japan Physicians Association, ed.: Influenza Manual in 2011-2012 season (6th edition), *The Journal of Japan Physicians Association.* 2011;26 Suppl 2:15-21
24 After the completion of Study J307, the following discussion was made regarding the possible cause of the difference in the incidence of influenza virus infection in the placebo group between Study J307 and Study J306.
It is reported in published literature, etc., that the pandemic influenza A/H1N1 virus strain was spreading during the 2009/2010 season when Study J306 was conducted, and that infection with the pandemic influenza developed less frequently in parent generation, while the disease developed more frequently in children in their teens (Morgan OW et al. *Emerg Infect Dis.* 2010;16(4):631-637, Odaira F et al. *Euro Surveill.* 2009;14(35):pii: 19320, Kawai N et al. *J Infect Chemother.* 2011;17:375-381). In Study J306, the incidence of the influenza in the placebo group stratified by age (in population corresponding to the FASIINAB) was 13.8% (4 of 29 subjects) in those in their teens, whereas the incidence was 5.5% (4 of 73 subjects) in those aged 30 to 39 years and 0% (0 of 45 subjects) in those aged ≥40 years, showing a decrease in the incidence with age. In this study, subjects of parent generation, i.e., those aged ≥30 years, accounted for approximately 70% of all the enrolled subjects, which is likely to have contributed to the lower incidence in the placebo group compared with Study J307.

days after the administration of the study drug. According to a report, when healthy adults were experimentally inoculated with influenza virus, virus shedding reached a peak 2 days after the inoculation, with the mean duration of virus shedding being 4.8 days.[25)] These findings suggested that virus shedding in index case patients with influenza virus infection increased for several days after the onset of symptoms, and this period is therefore critical for an antiviral drug against influenza to exhibit a prophylactic effect. In order to see a daily trend of disease onset in Study J306, changes in the cumulative incidence of laboratory-confirmed influenza virus infection (in the population equivalent to FASIINAB) was investigated. The cumulative incidence of influenza virus infection from the start of treatment up to Day 5 was 3.6% (7 of 197 subjects) in the laninamivir octanoate 20 mg group, 3.2% (6 of 188subjects) in the laninamivir octanoate 40 mg group, and was 3.8% (7 of 183 subjects) in the placebo group, suggesting that laninamivir octanoate was not effective enough during the period when virus shedding in index case patients increased.

Based on these findings, it was assumed that an adequately maintained laninamivir octanoate concentration in the target tissue is imperative to improve the prophylactic effect of laninamivir octanoate, for which the dose or dosing frequency would have been increased. However, Study J306 revealed the similar incidences of laboratory-confirmed influenza virus infection between the laninamivir octanoate 20 mg group and the laninamivir octanoate 40 mg group, which suggested that higher dose would not necessarily improve the prophylactic effect. Therefore, in Study J307, laninamivir octanoate was administered not only on Day 1 but also on Days 2 and 3 as more frequent virus shedding was expected in index case patients on these days, and the dose remained at 20 mg.

PMDA considers as follows:
Taking account of the observation that, In Study J108, laninamivir octanoate concentrations exceeding the IC_{50} value were maintained in alveolar epithelial lining fluid and in alveolar macrophages for an extended period. Study J306 suggested a likely inhibitory effect of laninamivir octanoate on the onset of laboratory-confirmed influenza virus infection when administered once weekly at the dose of 20 mg or 40 mg. The efficacy of single dose inhalation of laninamivir octanoate (40 mg in adults) was demonstrated in the treatment of influenza virus infection. Based on these findings, the possibility cannot be completely ruled out that a single dose inhalation of laninamivir octanoate is effective in the prophylaxis of influenza virus infection. In Study J307, single dosing should also have been examined from the aspect of convenience in prophylactic use of the drug, apart from once-daily dosing for 2 or 3 days.

The dosing regimen of Study J307 was not based on the pharmacokinetic data (drug concentrations in alveolar epithelial lining fluid and in alveolar macrophages) following once-daily dosing for 2 or 3 days. Nevertheless, dose and administration including the duration of treatment should be determined in a way that the prophylactic effect of the drug is optimized, with consideration of the likely period of exposure to influenza virus shed by the index case patient. Therefore, given the result of Study J306 and discussion made by the applicant, the choice of multiple dosing for 2 or 3 days is understandable, and the dosing regimen of 20 mg once daily for 2 or 3 days used for the evaluation of the efficacy and the safety of laninamivir octanoate in Study J307 is acceptable.

However, apart from the dosage and administration, there were some other changes in the design of Study J307. Impacts of these changes on the study are discussed in the next section.

25) Carrat F et al. *Am J Epidemiol*. 2008;167:775-785

(b) Changes in other than dosage and administration

PMDA asked the applicant to explain the changes made to the study design of Study J307 from Study J306, apart from dosage and administration.

The applicant explained as follows:

Table 12 shows the differences in the study design between Study J306 and Study J307.

Table 12. Differences in study design between Study J306 and Study J307

Change	Study J306	Study J307
Inclusion criteria for index case patients with influenza virus infection	Subjects who do not live with a family member or other who was infected with influenza A or B virus within 4 weeks before consent.	Subjects who were the first to be infected by influenza A or B virus among family members or others living together since [redacted] 20[redacted].
Inclusion criteria for subjects		
Confirmation of no symptoms of influenza virus infection	Subjects who tested negative by an influenza virus kit.	Clinical diagnosis by physician (diagnosis by kit not specified)
Competence in inhaling the drug with the use of a dedicated inhaler	Subjects considered competent to inhale the drug	Not specified
Age	Not specified	≥10 years (at consent)
Exclusion criteria for subjects		
Self-rating of symptom	Subjects unable to declare the presence or absence of symptoms of influenza (pyrexia, headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough)	Not specified
Influenza vaccination	Not specified	Subjects who received influenza vaccine in [redacted] 20[redacted] and thereafter
History of influenza virus infection	Subjects who had symptoms of influenza A or B virus infection in [redacted] 20[redacted] and thereafter	Not specified
Other		
The population used for primary efficacy analysis	FAS All subjects enrolled in the clinical study, excluding those listed below, were included in the full analysis set (FAS), 1) Major GCP violation (violation of informed consent, serious violation in study procedure) 2) Subjects who never received the study drug 3) Subjects with no observation data for the evaluation of the onset of influenza virus infection after randomization 4) Subjects whose index case patients tested negative by an influenza virus kit at consent 5) Subjects who tested positive by an influenza virus kit at consent	FASIINAB Of subjects in the FAS, those who tested negative by viral PCR test at enrollment and their index case patients living together tested positive were included in FASIINAB.
Prohibited concomitant drugs	Antiviral drugs for influenza (amantadine hydrochloride, zanamivir hydrate, oseltamivir phosphate)	Antiviral drugs for influenza (amantadine hydrochloride, zanamivir hydrate, oseltamivir phosphate, peramivir hydrate for injection, laninamivir octanoate hydrate, other drugs indicated for influenza virus infection [e.g., Maoto])
Treatment for index case patients (specification of antiviral drugs to be used)	Not specified	Oseltamivir phosphate, as a rule (zanamivir hydrate may be used in children aged 10 to 19 years)
Monitoring of subjects after the onset of symptoms	When influenza virus infection was diagnosed by an influenza virus kit or based on medical judgment on clinical symptoms, etc., the study was to be terminated at that point.	Not specified.
Symptom card/subject diary	To be recorded once daily before bedtime according to a 2-grade rating scale (no/yes).	To be recorded twice daily in the morning and in the evening according to a 4-grade rating scale (none/mild/moderate/severe)
Viral PCR test	RT-PCR Identification of type and subtype: Type AH1, AH3, and B → Measurement of amplification length by electrophoresis Type AH1-2009 → Fluorescence detection by real-time RT-PCR	RT-PCR Identification of type and subtype: All types and subtypes → Measurement of amplification length by electrophoresis
Influenza assessment committee members	Not appointed	Appointed

The reasons for the changes in the study design from Study J306 to that of Study J307 are described below.

In the inclusion criteria of Study J306, there was no particular age restriction for enrollment, and patients who were competent to take the drug using the dedicated inhaler were considered eligible regardless of age. In Study J307, in contrast, eligible patients were ≥10 years old. Because of changes in the recording method for the subject diary, children aged <10 years were excluded from the study for their assumed difficulty in performing self-rating of influenza symptoms accurately. Those who were not able to declare the symptoms specified in the exclusion criteria were also excluded from the study for the same reason.

In Study J306, subjects were required to be tested negative with an influenza virus kit so that enrollment was restricted only to uninfected subjects. However, of 612 subjects who provided consent in Study J306, only 1 subject was found positive for the test with an influenza virus kit at the time of consent, so it was determined the confirmation of "the absence of influenza virus infection" could be made based on a clinical diagnosis by a physician alone.

Assuming prophylactic antiviral drugs against influenza are likely to be used regardless of the patient's history of vaccination in routine clinical settings, vaccination history was not mentioned in the criteria of Study J306. In Study J307, however, subjects who were vaccinated for influenza in or after [redacted] 20[redacted] were excluded so that the true prophylactic effect of laninamivir octanoate could be evaluated.

In Study J306, of the subjects enrolled in the study, those who had major GCP violation, who did not receive the study drug, or who had no efficacy data were excluded from analysis, and the remaining subjects were included in the full analysis set (FAS), which was to be used for the efficacy analysis. The incidences of laboratory-confirmed influenza virus infection were analyzed by the result of viral PCR at enrollment. The incidences of influenza virus infection in viral PCR-negative subjects in the laninamivir octanoate 20 mg once weekly group, the laninamivir octanoate 40 mg once weekly group, the placebo group were 3.5% (7 of 198 subjects), 3.7% (7 of 189 subjects), and 6.5% (12 of 184 subjects), respectively, whereas the incidences in viral PCR-positive subjects in these groups were 33.3% (3 of 9 subjects), 18.8% (3 of 16 subjects), and 35.7% (5 of 14 subjects), respectively. This suggested the presence of a high-risk subgroup in the FAS and its possible impact on efficacy evaluation. Therefore, in Study J307, of subjects in the FAS, those who were tested negative by viral PCR test at enrollment while their index case patients in contact were tested positive by viral PCR test at enrollment were referred to as FAS index infected virus negative at baseline (FASIINAB), which was to be used for the efficacy analysis.

Some changes were made in efficacy-related parameters such as the observation period, follow-up frequency,[26)] and severity criteria for the symptoms[27)] for the purpose of improving the accuracy in the confirmation of the onset of influenza virus infection, by which the course of illness before and after symptom onset would be grasped in more detail so that medical experts and influenza assessment committee members were able to determine the onset date of the symptoms more accurately.

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26) Subjects were monitored for body temperature and influenza symptoms once daily before bedtime in Study J306 and twice daily in the morning and in the evening in Study J307.

27) In Study J306, symptoms were rated in 2 grades (yes/no). Symptoms interfering with the activities of daily living were defined as "yes (symptomatic)." In Study J307, symptoms were rated in 4 grades (none/mild/moderate/severe). Moderate and severe symptoms (i.e. those interfering with the activities of daily living) were defined as "symptomatic."

In Study J307, after the changes were made in the recording method for the subject diary, the courses of influenza symptoms were provided in more details. The influenza assessment committee was established to perform more objective assessment of the onset of influenza virus infection based on the provided details. The clinical study protocol stipulates the role of the influenza assessment committee members as "to give advice on the assessment and classification of influenza virus infection from a medical aspect, based on the result of a viral PCR test, body temperature, and time-course of influenza symptoms of a subject who developed influenza symptoms." A final decision was made by discussions between the sponsor and medical experts before data locking, as was the case with Study J306.

PMDA considers as follows:
The modification was made in the study design of Study J306 prior to the conduct of Study J307 because Study J306 failed to demonstrate the prophylactic effect of laninamivir octanoate against influenza virus infection. Therefore, the efficacy and safety of laninamivir octanoate may be evaluated to a certain extent, based on the result of Study J307. Even so, the following issues should have been taken into consideration. Detailed discussion is given in sections "4.(iii).B.(1).2) Efficacy evaluation in Study J307" and "4.(iii).B.(4) Dosage and administration."

(a) Analysis sets
The absence of influenza virus in a subject is usually confirmed based only on the clinical diagnosis by a physician in clinical practice, and it seems difficult to require a confirmed diagnosis by viral PCR test prior to the prophylactic use of laninamivir octanoate. Inclusion of subjects in the FASIINAB involves viral PCR test results, and therefore the efficacy analysis should use the FAS rather than the FASIINAB in less need.

(b) Study subjects
Subjects who received influenza vaccination were excluded from the study. However, high-risk patients have undergone vaccination against influenza in general and laninamivir octanoate is highly likely to be administered to these patients. Therefore, the efficacy and safety of laninamivir octanoate should have been also investigated in vaccinated subjects.

Only children aged ≥10 years were included in the study because of the anticipated difficulty for children aged <10 years performing accurate self-rating of influenza symptoms. It is convincing that young children have difficulty identifying the symptoms in the same way adults do. Nevertheless, symptom recording methods could be developed for each age group, according to the level of understanding, or the patient's condition could be observed and confirmed by a parent or guardian of the patient. Such strategies could have made possible the assessment of the onset of influenza virus infection. Thus, the evaluation of the prophylactic effect of laninamivir octanoate in young children was feasible.

4.(iii).B.(1).2) Efficacy evaluation in Study J307
In Study J307 where the ITT (intention-to-treat),[28)] FAS, and FASIINAB were used for the efficacy analysis, the incidences of laboratory-confirmed influenza virus infection were as shown in Table 13.

[28)] Randomized subject population, excluding 4 subjects with GCP violation

Table 13. Incidences of laboratory-confirmed influenza virus infection by analysis set (Study J307)

Analysis set	Treatment group	No. of subjects	No. of infected subjects (%)	*P* value[a)]	Rate of decrease in relative risk[b)] (%)
ITT	Laninamivir octanoate 20 mg × 2 group	568	30 (5.3)	<0.0001	74.3
	Laninamivir octanoate 20 mg × 3 group	565	31 (5.5)	<0.0001	73.3
	Placebo group	574	118 (20.6)	-	-
FAS	Laninamivir octanoate 20 mg × 2 group	550	29 (5.3)	<0.0001	74.2
	Laninamivir octanoate 20 mg × 3 group	550	31 (5.6)	<0.0001	72.4
	Placebo group	558	114 (20.4)	-	-
FASIINAB	Laninamivir octanoate 20 mg × 2 group	487	19 (3.9)	<0.0001	77.0
	Laninamivir octanoate 20 mg × 3 group	486	18 (3.7)	<0.0001	78.1
	Placebo group	478	81 (16.9)	-	-

a) Fisher's exact test using the placebo group as control
b) 100 × (1 – incidence in the laninamivir octanoate group / incidence in the placebo group)

The protocol of Study J307 stipulates that the efficacy endpoints "should be classified based on the results of viral PCR test, body temperature, and the severity of each influenza symptom (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough), upon discussion with medical experts and the influenza assessment committee members before data locking." PMDA asked the applicant to explain the changes made in initial classification and reasons for the changes in some subjects, based on the discussion between the sponsor and the medical experts.

The applicant explained as follows:
In Study J307, changes in the classification of efficacy endpoints were made in 10 subjects. In 9 of these subjects, "symptomatic influenza virus infection[29)]" was changed to "asymptomatic influenza virus infection.[30)]" The remaining 1 subject was in the laninamivir octanoate 20 mg once daily 2-day dose group and was initially classified into "laboratory-confirmed influenza virus infection,[31)]" which was changed after discussion among the medical experts and 2 influenza assessment committee members. The subject was positive by viral PCR test on Day 1 and had pyrexia and moderate influenza symptoms from Day 7 onward, based on which laboratory-confirmed diagnosis of influenza virus infection was made on Day 7. However, the pyrexia and other symptoms observed on and after Day 7 were considered not influenza-induced because the PCR test result was negative both on Day 7 and Day 11. It was concluded that there was no relationship between the PCR test results on Day 1 and the symptoms on and after Day 7 and that the efficacy endpoint classification was "asymptomatic influenza virus infection." If the classification had remained as "laboratory-confirmed influenza virus infection" as assessed initially, the incidence of laboratory-confirmed influenza infection in the FAS would have been 5.5% (30 of 550 subjects) with the rate of decrease in relative risk being 73.3%. This would have been a statistically significant decrease in the incidence as compared with the placebo group ($P < 0.0001$, Fisher's exact test).

PMDA considers the efficacy of laninamivir octanoate as follows:
In Study J307, final decisions on the "laboratory-confirmed influenza virus infection" were made based on the discussion between the sponsor and the medical experts before data locking.

29) Defined as subjects tested positive by viral PCR who had body temperature ≥37.5°C and any of 7 influenza symptoms (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough).
30) Defined as subjects tested positive by viral PCR who had body temperature ≥37.5°C and did not show any of 7 influenza symptoms (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough).
31) Defined as subjects tested positive by viral PCR who had body temperature ≥37.5°C and showed ≥2 of the 7 influenza symptoms (headache, myalgia or arthralgia, fatigue, chills or sweaty, nasal symptoms, sore throat, cough).

However, efficacy evaluation should have been performed according to the pre-determined evaluation criteria. Nevertheless, even the initial classification would contribute to a statistically significant decrease in relative risks with laninamivir octanoate as compared with placebo, and the results were similar between the ITT and FAS. PMDA therefore concluded that the efficacy of laninamivir octanoate was demonstrated.

4.(iii).B.(1).3) Efficacy by viral type

The incidences of laboratory-confirmed influenza virus infection by viral type and subtype in index case patients in Study J306[32] and in Study J307 are shown in Tables 14 and 15.

Table 14. Incidences of laboratory-confirmed influenza virus infection by viral type and subtype in index case patients (Study J306, population equivalent to FASIINAB)

Viral type/subtype in index case patients	Laninamivir octanoate 20 mg group			Laninamivir octanoate 40 mg group			Placebo group
	Incidence	*P* value[a]	Rate of decrease in relative risk[b] [95% CI]	Incidence	*P* value[a]	Rate of decrease in relative risk[b] [95% CI]	Incidence
AH1-2009	3.6% (7/197)	0.2393	45.8% [-34.6, 78.2]	3.7% (7/188)	0.2454	43.2% [-41.0, 77.1]	6.6% (12/183)

a) Fisher's exact test using placebo group as the control
b) 100 × (1 – incidence in the laninamivir octanoate group / incidence in the placebo group)

Table 15. Incidences of laboratory-confirmed influenza virus infection by viral type and subtype in index case patients (Study J307, FASIINAB)

Viral type/subtype in index case patients	Laninamivir octanoate 20 mg × 2 group			Laninamivir octanoate 20 mg × 3 group			Placebo group
	Incidence	*P* value[a]	Rate of decrease in relative risk[b] [95% CI]	Incidence	*P* value[a]	Rate of decrease in relative risk[b] [95% CI]	Incidence
AH3	3.6% (16/443)	<0.0001	79.1% [64.7, 87.6]	3.2% (14/440)	<0.0001	81.6% [67.9, 89.4]	17.3% (75/434)
B	7.0% (3/43)	0.4833	50.0% [-87.1, 86.6]	9.1% (4/44)	0.5210	34.8% [-114.9, 80.2]	14.0% (6/43)

a) Fisher's exact test using placebo group as the control
b) 100 × (1 – incidence in the laninamivir octanoate group / incidence in the placebo group)

Since Study J307 had revealed lower decrease rates of relative risks in index case patients with influenza B virus in the both dose groups as compared with those with AH3 virus, PMDA asked the applicant whether or not laninamivir octanoate was effective in preventing influenza B virus infection.

The applicant explained as follows:
The sensitivity of clinical isolates to laninamivir octanoate was lower in influenza B virus than in influenza A virus [see "3.(i).B.(2) Sensitivity of clinically isolated influenza virus strains to laninamivir octanoate in recent years"], suggesting that the different sensitivity levels of influenza A and B viruses may have been contributory to prophylactic effect on the each virus. However, despite the small number of index case patients with influenza B virus in Study J307, laninamivir octanoate exhibited a trend of clinical prophylactic effect against B virus infection similar to that against AH3 virus. Therefore laninamivir octanoate is expected to be effective in preventing influenza B virus infection as well.

PMDA considers the prophylactic effect of laninamivir octanoate by viral type and subtype as follows:

[32] In Study J306 which was conducted during the epidemic season in 2009, influenza A H1N1 virus strain (AH1-2009) accounted for 100% of the virus isolated from index case patients.

In Study J306, the incidences of laboratory-confirmed influenza virus infection were 3.6% (7 of 197 subjects) in the laninamivir octanoate 20 mg group, 3.7% (7 of 188 subjects) in the laninamivir octanoate 40 mg group, and was 6.6% (12 of 183 subjects) in the placebo group, showing a trend toward lower incidences in the laninamivir octanoate groups as compared with the placebo group, although the study was conducted with the dosing regimen modified from the proposed dosage and administration. Also, nonclinical studies showed that the antiviral activity of the drug against AH1-2009 virus was similar to that against clinical strains isolated before 2009 [see "3.(i).B.(2) Sensitivity of clinically isolated influenza virus strains to laninamivir octanoate in recent years"]. Based on these findings, laninamivir octanoate is assumed to have a certain degree of prophylactic effect against AH1-2009 virus.

In Study J307, the decrease rate in relative risks was lower in index case patients with influenza B virus infection as compared with those with AH3 virus infection, regardless of the dosing regimen of laninamivir octanoate. This may be partly attributable to the small number of index case patients with B virus infection in the study while the clinical strain of influenza B virus tended to be less sensitive to laninamivir octanoate than that of influenza A virus. Thus, taking account of the similar trends in the clinical prophylactic effects against influenza B virus and AH3 virus, laninamivir octanoate is considered to have a certain degree of efficacy against influenza B virus as well.

However, given epidemic influenza virus strains varying from season to season, information on the efficacy of laninamivir octanoate in index case patients should be further collected by virus type through the post-marketing surveillance, and obtained information should be promptly provided to clinical practice.

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

4.(iii).B.(2).1) Safety in safety analysis set

Adverse events with an incidence of ≥1% in any treatment group in Study J306 and in Study J307 were as shown in Table 16.

Table 16. Adverse events with an incidence of ≥1% in any group (Study J306, Study J307)

Treatment group	Study J306		Study J307		Laninamivir octanoate groups combined	Placebo groups combined
	Laninamivir octanoate 20 mg once weekly	Laninamivir octanoate 40 mg once weekly	Laninamivir octanoate 20 mg × 2	Laninamivir octanoate 20 mg × 3		
No. of subjects evaluated	207	205	552	553	1517	757
Adverse events	28 (13.5)	29 (14.1)	74 (13.4)	72 (13.0)	203 (13.4)	95 (12.5)
Diarrhoea	4 (1.9)	2 (1.0)	5 (0.9)	1 (0.2)	12 (0.8)	8 (1.1)
Nasopharyngitis	7 (3.4)	10 (4.9)	12 (2.2)	18 (3.3)	47 (3.1)	28 (3.7)
Headache	2 (1.0)	4 (2.0)	7 (1.3)	6 (1.1)	19 (1.3)	4 (0.5)
Upper respiratory tract inflammation	3 (1.4)	1 (0.5)	11 (2.0)	7 (1.3)	22 (1.5)	5 (0.7)

Number of subjects (%)

The applicant explained the safety in the prophylactic use of laninamivir octanoate against influenza virus infection as follows:

The incidence of adverse events was 13.4% (203 of 1517 subjects) in the combined laninamivir octanoate group and was 12.5% (95 of 757 subjects) in the combined placebo group, and the incidence of adverse drug reactions was 3.9% (59 of 1517 subjects) in the combined laninamivir octanoate group and was 2.5% (19 of 757 subjects) in the combined placebo group. The incidences of upper respiratory tract inflammation and headache tended to be higher in the combined laninamivir octanoate group than in the placebo group. There were no deaths or other serious adverse events. A severe adverse event (diarrhoea) occurred in the laninamivir octanoate 20 mg once weekly group but resolved after treatment.

Upper respiratory tract inflammation and headache, which were more frequent in the combined laninamivir octanoate group than in the placebo group, had no consistent trend in the incidences in each laninamivir octanoate group. These events are also associated symptoms of influenza virus infection, and the presence of these symptoms in a person infected with influenza virus was considered a confirmed case of influenza virus infection and was therefore assessed as efficacy endpoints, and these events were not reported as the adverse events. This may have resulted in higher incidences of upper respiratory tract inflammation and headache in the laninamivir octanoate groups.

PMDA considers the safety of laninamivir octanoate as follows:
More frequent upper respiratory tract inflammation and headache in the laninamivir octanoate group than in the placebo group are likely due to the reporting rule for these events. After all, the incidences of the events are not high and do not significantly affect the safety of laninamivir octanoate. Since the number of subjects treated with the proposed dosage and administration was small, safety information should be collected further.

4.(iii).B.(2).2) Abnormal behaviour in children and adolescents

In light of reported neuropsychiatric symptoms such as abnormal behaviour after the administration of antiviral drugs for influenza in children and adolescents, PMDA asked the applicant to explain whether or not the said symptoms were observed after the administration of laninamivir octanoate in clinical studies, or reported through the post-marketing surveillance or other studies.

The applicant explained as follows:
In clinical studies (Study J306, Study J307) conducted in Japan to investigate the prophylactic effect against influenza virus infection, adverse events such as delirium and abnormal behaviour were not observed.

In the use-results survey on laninamivir octanoate conducted after its approval for the treatment of influenza virus infection (November 1, 2010 to April 30, 2011), the incidence of adverse events related to abnormal behaviour/talk[33)] was 1.13% (40 of 3052 patients), with breakdowns of 3.1% (30 of 959 patients) in patients aged <10 years, 0.7% (8 of 1088 patients) in patients aged ≥10 and <20 years, 0.1% (2 of 1431 patients) in patients aged ≥20 and <65 years, and 0% (0 of 64 patients) in patients aged ≥65 years. Abnormal behaviour possibly leading to accidents or harming other people was reported in 4 patients (3 patients aged <10 years, 1 patient aged ≥10 and <20 years), and a causal relationship between these behaviors and laninamivir octanoate could not be ruled out in patients aged <10 years.

PMDA considers as follows:
Neuropsychiatric symptoms such as abnormal behaviour have been observed in children and adolescents after being treated with antiviral drugs for influenza. Although adverse events such as abnormal behaviour were not observed in clinical studies on the prophylactic laninamivir octanoate against influenza virus infection, abnormal behaviour was observed after the administration of laninamivir octanoate in the post-marketing surveillance on the treatment of influenza virus infection. Therefore, close monitoring of the occurrence of abnormal behaviour should be continued. The eligible age range for treatment with laninamivir octanoate is discussed in "4.(iii).B.(4) Dosage and administration."

33) Adverse events (delirium, elevated mood, fear, hallucination, hallucination visual, inappropriate affect, phobia, restlessness, sleep terror, abnormal behaviour, crying, unresponsive to stimuli, gaze palsy) that come under any of the following 5 categories: "A: Abnormal behaviour that may lead to an accident or harming other people," "B: Hallucination visual, hallucination/confused sense," "C: Delirious utterances, sing a song, meaningless movement," "D: Scare, fear, get angry, start crying, laugh, amimia, unresponsiveness," and "E: Put anything into his/her mouth."

4.(iii).B.(3) Indication

Based on the result of Study J307, PMDA considers that it is acceptable to indicate laninamivir octanoate for "the prophylaxis of influenza A or B virus infection."

Nevertheless, the primary preventive measure for influenza virus infection is vaccination. The prophylactic use of laninamivir octanoate is a complement to preventive vaccination rather than an alternative. Unlike therapeutic use, prophylactic use of an antiviral drug against influenza in any population group may increase a risk of the emergence of a resistant virus strain. Being prone to serious complications once infected with influenza virus, the high-risk population should be the primary target of prophylactic laninamivir octanoate.

Therefore, the following discussion was made on the prophylactic use of the drug in the high-risk population.

4.(iii).B.(3).1) High-risk population

The applicant explained the definition of high-risk population and study results in this population as follows:

Elderly individuals aged ≥65 years and those with decreased immune function, metabolic disease, chronic respiratory illness, chronic renal impairment, or chronic heart disease come under the definition of high-risk population issued in 2006 by the Advisory Committee on Immunization Practices (ACIP) of the US. Since they are considered prone to aggravation after being infected by influenza virus, the prophylaxis of infection with the use of influenza antiviral drugs is important.[34)] Therefore, the group of patients with said conditions were defined as high-risk population for the investigation of the efficacy and safety in the prophylactic use of laninamivir octanoate against influenza virus infection in this population.

In Study J307, 3.0% (44 of 1451 subjects) of all subjects were classified in the high-risk population. The incidence of laboratory-confirmed influenza virus infection in the high-risk population, although obtained from a limited number of subjects, was 7.1% (1 of 14 subjects) in the laninamivir octanoate 20 mg once daily 2-day dose group and 0% (0 of 10 subjects) in the laninamivir octanoate 20 mg once daily 3-day dose group, as compared with 20.0% (4 of 20 subjects) in the placebo group. The result suggested that laninamivir octanoate was effective in preventing influenza virus infection, as with other subjects enrolled in the study. The incidence of adverse events was 7.3% (4 of 55 subjects) in the high-risk population who received laninamivir octanoate in Studies J306 and J307, and there was no trend toward higher incidence in the high-risk population as compared with the entire laninamivir octanoate group (13.4% [203 of 1517 subjects]). Adverse events in the entire laninamivir octanoate group were glucose urine present and white blood cell count increased in 2 patients each and CRP increased in 1 patient (including duplicate counting), and none of them were unique to the high-risk population, which suggested that there were no adverse events with any particular problem in the high-risk population.

Based on these findings, the applicant considers that there are no problems either in efficacy or safety in the prophylactic use of laninamivir octanoate in the high-risk population.

PMDA asked the applicant a reason for including "patients who have decreased immune function," in the high-risk population as intended population for laninamivir octanoate, while the said patient group is not included in the intended population of the other antiviral drugs against influenza for prophylactic use. PMDA also asked the applicant to explain the efficacy and safety of laninamivir octanoate in this patient group.

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34) Fiore AE et al, *MMWR Recomm Rep.* 2011;60(1):1-24

The applicant explained as follows:
When influenza virus infection develops in patients with various diseases with decreased immune function or those who are on corticosteroids or other immunosuppressants, the patients are at high risk for worsening the symptoms. Therefore, the Infectious Diseases Society of America of the US[35] and ACIP[34] include these immunocompromised patients in the high-risk population for influenza virus infection. In patients who have decreased immune function due to the underlying disease or drug therapy, it is very likely that vaccination fails to induce immunity against the virus, and the prophylaxis of the illness by antiviral drug against influenza is of high clinical significance, which is therefore highly needed in this patient population. Therefore, the applicant considered that patients with decreased immune function should be included in the high-risk population. However, laninamivir octanoate was not administered to patients who have decreased immune function in Study J306 or in Study J307, and the prophylactic effect and safety of laninamivir octanoate in this patient population therefore have not been established.

PMDA considers as follows:
The prophylactic effect of laninamivir octanoate against influenza virus infection in the high-risk population was investigated in only 44 subjects in Study J307. However, the incidence of laboratory-confirmed influenza virus infection was lower in the laninamivir octanoate group as compared with the placebo group, and the result was not significantly different from that observed in the entire subject population. Thus, the prophylactic effect of laninamivir octanoate is suggested. PMDA confirmed that there were no events requiring particular caution in the safety the high-risk population.

Given that patients with decreased immune function such as those receiving immunosuppressants have difficulty preventing viral growth and that the efficacy of the vaccine is considered to be lower as compared with those with normal immune function, the inclusion of these patients in the high-risk population for the prophylactic use of laninamivir octanoate against influenza virus infection is understandable. However, due to the reported emergence of resistant viruses after the administration of other influenza antiviral drugs[36),37),38),39),40)] and the absence of data on the efficacy or safety of laninamivir octanoate in this patient group, a decision on whether or not to include these patients in the high-risk population for laninamivir octanoate will be made after being discussed in the Expert Discussion.

Since only a small number of high-risk subjects were enrolled in Study J307 and the characteristics of the subjects are diverse, information on the safety and efficacy of the prophylactic use of laninamivir octanoate in this population should be collected after the market launch [see "4.(iii).B.(6) Post-marketing surveillance"].

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

4.(iii).B.(4).1) Adults and adolescents aged ≥10 years

The applicant explained the reason for selecting "inhalation of laninamivir octanoate 20 mg once daily for 2 days" for the dosage and administration, as follows:
In Study J307, the incidence of laboratory-confirmed influenza virus infection was statistically significantly lower in patients receiving laninamivir octanoate 20 mg once daily for 2 or 3 days as compared with the placebo group, demonstrating the efficacy of laninamivir octanoate 20 mg once daily for 2 or 3 days in preventing laboratory-confirmed influenza virus infection.

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35) Harper SA et al. *Clin Infect Dis*. 2009;48(8):1003-1032
36) Piralla A et al. *J Clin Virol.* 2013 Jun 27 doi: 10.1016/j.jcv.2013.06.003, 2013
37) van der Vries E et al. *PLoS Pathog.* 2013;9(5): e1003343
38) Hurt AC Et al. *Influenza Other Respi Viruses.* 2013;doi: 10.1111/irv.12108
39) Ghedin E et al. *J Infect Dis.* 2011;203(2):168-174
40) Carr S et al. *Pediatr Infect Dis J.* 2011;30(4):284-288

The incidences of laboratory-confirmed influenza virus infection were similar between the laninamivir octanoate 20 mg once daily 2-dose group and the laninamivir octanoate 20 mg once daily 3-dose group, showing no difference in efficacy by dosing frequency.

Based on these results, the applicant determined that laninamivir octanoate 20 mg once daily for 2 days, the dosing regimen with less frequent dosing, as the optimum dosage and administration for preventing influenza in family members and others living together with patients with influenza virus infection.

PMDA considers the dosage and administration as follows:
As discussed in "4.(iii).B.(1) Efficacy," the efficacy and the safety of a single dose of laninamivir octanoate in preventing influenza virus infection should also have been investigated. However, it is acceptable that the dosage and administration of laninamivir octanoate be determined as 20 mg once daily for 2 days.

4.(iii).B.(4).2) Children aged <10 years

Since children aged <10 years were not enrolled in Study J307, the efficacy and safety of laninamivir octanoate in this age group have not been investigated. Therefore, PMDA asked the applicant to explain the appropriateness of administering laninamivir octanoate to children aged <10 years for the prophylaxis of influenza virus infection.

The applicant explained as follows:
The onset of laboratory-confirmed influenza virus infection by age group in Study J307 was as shown in Table 17. In the laninamivir octanoate 20 mg × 2 group, no significant difference was observed in the efficacy among age groups, suggesting that the administration of laninamivir octanoate 20 mg once daily for 2 days would be effective in preventing influenza virus infection also in children aged <10 years, as with adults and children aged ≥10 years.

Table 17. Efficacy by age group in Study J307 (FASIINAB)

Age (years)	Treatment group	No. of subjects evaluated	No. of infected subjects	Onset (%)	Rate of decrease in relative risk (%)[a)]
All	Laninamivir octanoate 20 mg × 2	487	19	3.9	77.0
	Laninamivir octanoate 20 mg × 3	486	18	3.7	78.1
	Placebo	478	81	16.9	-
10-19	Laninamivir octanoate 20 mg × 2	61	2	3.3	64.6
	Laninamivir octanoate 20 mg × 3	67	7	10.4	-12.8
	Placebo	54	5	9.3	-
20-29	Laninamivir octanoate 20 mg × 2	36	1	2.8	85.4
	Laninamivir octanoate 20 mg × 3	37	3	8.1	57.4
	Placebo	42	8	19.0	-
30-39	Laninamivir octanoate 20 mg × 2	241	12	5.0	74.2
	Laninamivir octanoate 20 mg × 3	235	8	3.4	82.4
	Placebo	264	51	19.3	-
≥40	Laninamivir octanoate 20 mg × 2	149	4	2.7	81.4
	Laninamivir octanoate 20 mg × 3	147	0	0	100
	Placebo	118	17	14.4	-

a) 100 × (1 – onset in the laninamivir octanoate group / onset in the placebo group)

In Study J306, there was no lower age limit as an inclusion criterion, and the dosage and administration was "laninamivir octanoate 20 or 40 mg once weekly inhalation (twice in total)," which was different from the proposed dosage and administration. The onset rate of laboratory-confirmed influenza virus infection in children aged <10 years (in the population equivalent to FASIINAB) was 10.5% (2 of 19 subjects) in the laninamivir octanoate 20 mg once weekly group and 5.3% (1 of 19 subjects) in the laninamivir octanoate 40 mg once weekly group, both of which were lower as compared with 11.5% (3 of 26 subjects) in the placebo group.

The incidence of adverse events in children aged <10 years in Study J306 was 4.5% (1 of 22 subjects) in the laninamivir octanoate 20 mg once weekly group (total exposure during the observation period, 40 mg), 7.7% (2 of 26 subjects) in the laninamivir octanoate 40 mg once weekly group (total exposure during the observation period, 80 mg), and was 17.9% (5 of 28 subjects) in the placebo group, showing no trend toward a higher incidence in the laninamivir octanoate groups as compared with the placebo group.

In the clinical study in children aged <10 years, on which data were submitted as the data supporting the indication of "treatment of influenza A or B virus infection," only 6 children were treated with laninamivir octanoate 20 mg once daily for 2 days in the pediatric PK study[41)] (as the safety analysis set). However, the safety of single-dose of laninamivir octanoate 20 mg or 40 mg (study in patients aged ≤9 years,[42)] a pediatric PK study[41)]) was investigated. The incidence of adverse events in these patients was as shown in Table 18. All of the observed events were mild or moderate in severity, and none of the events posed any particular concern.

41) Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.7.6.5.7) (approved on September 10, 2010)

42) Summary of the data submitted in the application for Inavir Dry Powder Inhaler 20 mg for the indication of "Treatment of influenza A or B virus infection" (CTD 2.7.6.12.6) (approved on September 10, 2010)

Table 18. Incidence of adverse events in clinical studies to treat patients aged <10 years with influenza virus infection

Treatment group	Laninamivir octanoate 20 mg single dose	Laninamivir octanoate 40 mg single dose	Laninamivir octanoate 20 mg × 2	Oseltamivir phosphate
Number or patients evaluated	69	72	6	62
Adverse events	23 (33.3)	17 (23.6)	3 (50.0)	24 (38.7)
Adverse drug reactions	5 (7.2)	4 (5.6)	1 (16.7)	4 (6.5)

Number of patients (%)

In the use-results survey of laninamivir octanoate (November 1, 2010 to April 30, 2011) in the treatment of influenza virus infection, 959 children aged <10 years received the treatment (20 mg once in a single dose), and the incidence of adverse drug reactions/infectious diseases was 2.5% (24 of 959 patients).[43)]

Based on these findings, the applicant considers that inhalation of laninamivir octanoate 20 mg once daily for 2 days is expected to be effective in children aged <10 years with no particular safety problem.

The following is PMDA's view on the prophylactic use of laninamivir octanoate to children aged <10 years:
In Study J307, the efficacy and safety of laninamivir octanoate in children aged <10 years were not investigated. The approved dosage and administration of laninamivir octanoate for the treatment of influenza virus infection in children aged <10 years is a single dose inhalation of 20 mg. Considering lack of experiences with current proposed laninamivir octanoate 20 mg once daily for 2 days and resulting increased exposure to the drug that is beyond the level at the therapeutic dose, investigation on the efficacy and the safety in children aged <10 years is less than adequate, and it is difficult to determine the dosage and administration in children of this age group for now. At the same time, it is undeniably true that there are children aged <10 years at high-risk for influenza virus infection and the prophylactic use of laninamivir octanoate in this age group is in demand. Therefore, adequate investigation on appropriate dose and administration for children aged <10 years and a subsequent early launch of the development of a product for the prophylaxis of influenza virus infection in this age group are urged.

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

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

The applicant explained the clinical positioning of laninamivir octanoate as follows:
Vaccination with influenza virus is the primary preventive measures against influenza virus infection. However, some remaining issues in vaccination include a possible mismatch between the available vaccine strain and the epidemic strain[23)] and a time lag after vaccination until an adequate amount of antibody is produced for preventing infection.[44)] Therefore, for those who have a high risk factor whose symptoms of infection are often aggravated, the post-contact administration of a prophylactic antiviral drug is recommended.

The prophylactic use of antiviral drugs against influenza is of high significance as a preventive measure in high-risk people post-contact or immediately after the outbreak of a pandemic, and so is as an additional treatment option. Whereas the existing drugs takes 10 days to obtain a post-contact prophylactic effect with once-daily dose, laninamivir octanoate takes only 2 days. Also,

43) Kashiwagi S et al. *Int J Antimicrob Agents*. 2012;40(5):381-388
44) The Japanese Society for Vaccinology, ed., *Vaccine Dictionary*. 2004;p.141-155

study results suggested that there were no particular problems in the efficacy or safety of the drug despite scant experiences in the prophylactic use in those who have a high risk factor. Therefore, the applicant considers that providing with clinical practice with prophylactic laninamivir octanoate is of significance.

PMDA considers the clinical significance of laninamivir octanoate as follows:
There are only a limited number of antiviral drugs against influenza effective for the prophylaxis of the disease after contact with influenza virus. Laninamivir octanoate works to complement vaccine-based prophylaxis in those who have a high risk factor. Therefore, it is of significance to provide clinical practice with laninamivir octanoate as an option that is expected to be effective for the prophylaxis of influenza virus infection.

4.(iii).B.(6) Post-marketing surveillance

The applicant explained the post-marketing surveillance as follows:
Based on the discussion in "4.(iii).B.(3).1) High-risk population," the applicant plans to conduct post-marketing surveillance in the elderly in the high-risk population.

The reasons for targeting the elderly as high-risk population in the surveillance described below.

(a) In Studies J306 and J307, only 55 high-risk subjects were included in the laninamivir octanoate group despite efforts to enroll as many in the high-risk population as possible.

(b) The "Recommendation from the Japanese Association for Infectious Diseases 2012 – How to control nosocomial infection of influenza – (including the infection in elderly facilities)"[45)] encourages the proactive and early use of antiviral drugs for the prophylaxis of influenza virus infection, as a means to minimize risks in hospitals, particularly in elderly facilities. In general, these institutions are cooperative in the conduct of surveillance.

(c) A large amount of data can be obtained from many inpatients or residents of one facility.

(d) The elderly are more likely to have other high-risk factors.

PMDA considers as follows:
The high-risk population includes patients with diverse characteristics, and the safety and efficacy of laninamivir octanoate have not been adequately investigated in such patients. Therefore, information should be collected not only from the elderly but also from other high-risk populations. At the same time, due to the possible emergence of a resistant influenza virus strain associated with the prophylactic use of laninamivir octanoate, a trend of emergence of laninamivir octanoate-resistant strains should be investigated further.

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

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

To be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, PMDA concludes that the efficacy of Inavir (laninamivir octanoate) in the prophylaxis of influenza A or B virus infection was demonstrated and its safety is

45) http://www.kansensho.or.jp/influenza/1208_teigen.html

acceptable in view of its observed benefits. The efficacy and safety in high-risk patients should be investigated in the post-marketing surveillance. For this application, the efficacy and safety of the prophylactic use of laninamivir octanoate against influenza virus infection were not investigated in children aged <10 years. However, it is of significance to prevent influenza virus infection in these patients, and an early launch of development is urged.

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)

November 1, 2013

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]	November 15, 2012

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. 8/2008 dated December 25, 2008).

The PMDA's conclusions described in Review Report (1) were generally supported by the Expert Discussion. PMDA conducted an additional review of the following points and took necessary actions.

(1) Indication

The PMDA's conclusion on the indication [see Review Report (1) "4.(iii).B.(3) Indication"] was supported by expert advisors in the Expert Discussion, while the following comments were raised by expert advisors:

- In terms of the prophylaxis of influenza B virus infection, there were only a limited number of subjects investigated in Study J307 which was conducted according to the proposed dosage and administration. Also, the prophylactic effect of laninamivir octanoate on infection tended to be lower against influenza B virus as compared with that against influenza A virus. Therefore, there is a lack of robust evidence to support the prophylactic effect of laninamivir octanoate against influenza B virus infection. There is no objection to approve the prophylactic use of laninamivir octanoate against influenza B virus infection because of its effect in theory. However, considering that sensitivity to laninamivir octanoate tends to be lower in type B clinical isolates than in type A clinical isolates, the study data should be provided to healthcare professionals in clinical practice in an appropriate manner once available.

- While it is understood that there are no efficacy or safety data on laninamivir octanoate in those who have decreased immune function, the demand is high for the prophylactic use of the drug in this population. The absence of efficacy and safety data in this population is also true with the similar drugs, and those who have decreased immune function is not listed as intended population in the package inserts of these drugs. Therefore, they should inevitably be regarded in a similar way for laninamivir octanoate. However, this never means that laninamivir octanoate is contraindicated in those who have decreased immune function, which should not be misunderstood.

Taking account of comments from the expert advisors, PMDA conducted the following reviews and obtained their approval.

In Study J307 that evaluated the prophylactic effect against influenza B virus infection, a decrease in the incidence of laboratory-confirmed influenza virus infection was observed. In the treatment of influenza virus infection, laninamivir octanoate showed a certain degree of efficacy against influenza B virus infection.[46)] PMDA therefore considers that laninamivir octanoate has an inhibitory effect against influenza B virus. However, in response to the comments from the expert advisors and considering the need for providing healthcare professionals in clinical practice with the data on the prophylactic effect on different virus types observed in Study J307, PMDA instructed the applicant to include the said data in the package insert and the applicant agreed.

No data are available on the efficacy or safety of laninamivir octanoate in those who have decreased immune function for now. Therefore, it is difficult to include these patients as high-risk population in the intended population in the package insert. However, PMDA understands that there are patients who have decreased immune function in the elderly aged ≥65 years and patients who have metabolic disease, chronic respiratory illness, chronic renal impairment, or chronic heart disease, and does not deny the prophylactic use of the drug in these patients. The applicant plans to prepare informative materials that provide relevant information with a caution to avoid misunderstanding. After all, PMDA concluded that the administration of laninamivir octanoate should be allowed to those who have decreased immune function, a group of patients with a high need for prophylactic antiviral agents against influenza, by adding the term "as a rule," in the statement in the "Precautions for Indications" section of the package insert, as with the similar drugs.

(2) Dosage and administration

The PMDA's conclusion on the dosage and administration [see Review Report (1) "4.(iii).B.(4) Dosage and administration"] was supported by the expert advisors, and the following additional comments were made:

- There is no justification for the denial of dosage and administration used in Study J306. Given the dosage and administration of laninamivir octanoate for the treatment of influenza virus infection, the possibility of single dosing should have also been examined in expectation of its prophylactic effect.

- Given the cumbersome method for the inhalation of laninamivir octanoate, single dose inhalation will be more convenient. A product should be developed for single dosing if its efficacy is promising.

- Because the efficacy and safety of laninamivir octanoate have not been studied in children aged <10 years, the expert advisors understand the present difficulty in approving the use of laninamivir octanoate in this age group. However, considering the presence of children in this age group who are at high risk for influenza virus infection, and it is appropriate to request the applicant to promote the development of a product indicated for this population.

Taking account of the comments raised from the expert advisors, PMDA instructed the applicant to launch the development of a product indicated for children aged <10 years and for single dose inhalation. The applicant agreed to the both instructions.

(3) Post-marketing surveillance

The PMDA's conclusion on the post-marketing surveillance [see Review Report (1) "4.(iii).B.(6) Post-marketing surveillance"] was supported by the expert advisors, and the following additional comments were made:

[46)] Review Report of Inavir Dry Powder Inhaler 20 mg (July 7, 2010)

- There is no sufficient data on the administration of laninamivir octanoate to those who have a high-risk factor, who are essentially subject to the prophylaxis of influenza virus infection. Therefore, the planned sample size of the post-marketing surveillance should be determined not only for the entire high-risk population but also for each subgroup of high-risk factors so that the efficacy and safety of the drug product can be evaluated factor-by-factor.

- The investigation of the prophylactic effect of laninamivir octanoate against influenza B virus infection should be continued.

In response to the comments of the expert advisors, PMDA instructed the applicant to determine the sample size of each subgroup of high-risk factors to be surveyed through the post-marketing surveillance and to investigate the prophylactic effect against influenza B virus infection.

In response to the instructions of PMDA, the applicant explained that the post-marketing surveillance would be conducted according to the plan as outlined in Table 19. The applicant also explained that the sample size of each high-risk factor was determined while considering the current feasibility of the survey, but efforts would be made to enroll as many subjects as possible. The applicant further explained that data on the prophylactic effect against influenza B virus would be collected from approximately 100 subjects out of the planned sample size of 500, based on the fact that influenza B virus accounted for approximately 20% of the virus strains isolated in the past 2 seasons (2011/2012, 2012/2013).

Table 19. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety and efficacy of laninamivir octanoate in the prophylactic use in high-risk subjects such as the elderly.
Survey method	Central registry system. To be conducted in 15 to 20 elderly facilities.
Patients population	The elderly (including high-risk subjects who have a high-risk factor)
Observation period	10 days from the start of the inhalation of laninamivir octanoate
Planned sample size	500 (including 10 patients with chronic respiratory illness, 30 patients with chronic heart disease, 30 patients with metabolic disease, 30 patients with renal impairment)
Priority investigation item	Patient background characteristics, viral type, laboratory test values, presence/absence of influenza symptoms

PMDA accepted the above post-marketing surveillance plan (draft).

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, 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

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 (5.3.5.1-1, 5.3.5.1-2). As a result, PMDA has concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of the above review, PMDA concludes that Inavir (laninamivir octanoate) may be approved after modifying the descriptions of indication and the dosage and administration as shown below. The re-examination period should be equal to the remaining period of the 8-year re-examination period determined for the indication for the treatment of influenza virus infection (until September 9, 2018).

[Indication]

Treatment and prophylaxis of influenza virus A or B infection

(The underlined part denotes an addition.)

[Dosage and administration]

1. Therapeutic use

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.

2. Prophylactic use

Adults and children aged ≥10 years:

Laninamivir octanoate 20 mg is administered by inhalation once daily for 2 days.

(The underlined parts denote additions.)