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The safety and efficacy of the long-acting neuraminidase inhibitor laninamivir octanoate hydrate for Inhalation Suspension Set in children under the age of 5 in a post-marketing surveillance

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ABSTRACT

Introduction: We conducted a post-marketing surveillance of laninamivir octanoate hydrate for Inhalation Suspension Set in patients under the age of 5 infected with the influenza virus to evaluate safety and efficacy of the drug.

Methods: Subjects enrolled by the centralized enrollment system were administered laninamivir once using a nebulizer based on the package insert.

Results: Safety was evaluated in 1104 patients. The incidence of ADRs was 1.00% (11/1104). Compared to the incidence of ADRs of 2.04% (9/441) in the clinical trials for development, no increase in the frequency of ADRs was noted. Serious ADRs were noted in 3 patients (5 cases): 2 cases of convulsive attack, each 1 case of muscular weakness, a depressed level of consciousness, and pain in extremities. Excluding 2 patients with unknown outcomes, all of the patients recovered or their symptoms were alleviated. To detect risk factors for the occurrence of ADRs, 16 attributes were examined, and none of them were found to be significant. Efficacy was evaluated in 881 patients. The median time (95% CI) to fever resolution was 37.0 (33.0–39.0) h in type A virus (785 patients), 45.0 (34.0–56.0) h in type B virus (95 patients), and 22.0 h (1 patient) in the mixed type. This was similar to the time to fever resolution in the clinical trials.

Conclusion: The results of this surveillance verified that there are no noticeable problems with the safety or efficacy of laninamivir for children under the age of 5 infected with the influenza A and B viruses.

1. Introduction

Laninamivir octanoate hydrate (laninamivir) is a long-acting neuraminidase (NA) inhibitor discovered and developed by Daiichi Sankyo Co., Ltd. in Japan. An inhaled powder (brand name: Inavir Dry Powder Inhaler) with laninamivir as its active ingredient was approved for the treatment of influenza A or B virus infection in October 2010 [1,2], and for prevention in December 2013 and August 2016 [3–5]. However, the Inavir Dry Powder Inhaler is administered via forced inspiration by patients themselves, therefore it was difficult to use for children under the age of 5, patients with respiratory diseases (e.g. bronchial asthma, or chronic obstructive pulmonary disease), or patients with an inadequate understanding of inhalation procedures [6]. Moreover, Inavir contains lactose hydrate as an excipient, therefore caution was required when it was used by patients with a history of hypersensitivity to dairy products. In order to improve these problems, an inhalation suspension preparation without lactose hydrate that allows delivering the drug to the target site (e.g. airway) via spontaneous breathing by using a nebulizer was developed. Approval for its manufacture and marketing was obtained in June 2019 (brand name: Inavir for Inhalation Suspension Set). To comprehend early the safety and efficacy of the drug in children under the age of 5, who are likely to often use it, we conducted a post-marketing surveillance from November 2019 to April 2020. This surveillance was done in accordance with Article 14-4, Para. 4 (Reexamination) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and "the Ministerial Order on Standards for Post-Marketing Surveillance and Test of Pharmaceuticals" (Ministry of Health, Labour, and Welfare Ordinance

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Table 1
Patient characteristics (patients evaluated for safety).

Attributes	Categories	Number of patients (%)	
Age (years)	0 [a]	87	(7.9)
	1	185	(16.8)
	2	191	(17.3)
	3	291	(26.4)
	4	350	(31.7)
Sex	Male	564	(51.1)
	Female	540	(48.9)
Body temperature at initial visit	<37.5°C	73	(6.6)
	37.5°C≤ <38.0°C	101	(9.1)
	38.0°C≤ <38.5°C	237	(21.5)
	38.5°C≤	693	(62.8)
	Minimum/median/maximum	36.0/38.7/41.3 (°C)	
	Mean ± standard deviation	38.7±0.8 (°C)	
Inpatient/Outpatient	Inpatient	0	(0.0)
	Outpatient	1104	(100.0)
Testing with a rapid diagnosis kit of influenza virus type	Influenza A	982	(88.9)
	Influenza B	118	(10.7)
	Mixed type	4	(0.4)
Total influenza symptoms score at initial visit [b]	≤3 pts	864	(78.3)
	4 pts≤	240	(21.7)
	Minimum/median/maximum	0/2.0/6 (pts)	
	Mean ± standard deviation	2.4 ± 1.3 (pts)	
Vaccination against influenza (after September 2019)	No	623	(56.4)
	Yes	365	(33.1)
	Unknown	116	(10.5)
History of febrile convulsion	No	1020	(92.4)
	Yes	58	(5.3)
	Unknown	26	(2.4)
History of allergies	No	918	(83.2)
	Yes	131	(11.9)
	Allergy to dairy products	24	(2.2)
	Others	110	(10.0)
	Unspecified	13	(1.2)
	Unknown	55	(5.0)
Underlying disease/complication	No	989	(89.6)
	Yes	114	(10.3)
	Hepatic disorder	1	(0.1)
	Renal disorder	0	(0.0)
	Unknown	1	(0.1)
High-risk underlying disease	No	1058	(95.8)
	Yes	45	(4.1)
	Chronic respiratory disease	45	(4.1)
	Chronic heart disease (except hypertension)	0	(0.0)
	Chronic metabolic disease including diabetes mellitus	0	(0.0)
	Diseases accompanied by reduced immune function	0	(0.0)
	Chronic renal impairment	0	(0.0)
	Unknown	1	(0.1)
Time from the onset of influenza to inhalation of laninamivir	≤12 h	393	(35.6)
	12 h< ≤24 h	464	(42.0)
	24 h< ≤36 h	135	(12.2)
	36 h< ≤48 h	48	(4.3)
	48 h<	30	(2.7)
	Unknown	34	(3.1)
	Minimum/median/maximum	0/15.0/108 (h)	
	Mean ± standard deviation	16.8±12.9 (h)	
Dosage of laninamivir	160 mg	1103	(99.9)
	20mg [c]	1	(0.1)

(*continued on next page*)

Table 1 (*continued*)

Attributes	Categories	Number of patients (%)	
Inhalation time of laninamivir	≤8 min	237	(21.5)
	8 min< ≤10 min	537	(48.6)
	10 min<	314	(28.4)
	Unknown	16	(1.4)
	Minimum/median/maximum	1/10.0/30 (min)	
	Mean ± standard deviation	10.7 ± 3.2 (min)	
Model of compressor used to inhale laninamivir	Recommended		
	PARI boy® SX	130	(11.8)
	PARI YPSITA®	0	(0.0)
	OMRON Compressor-type Nebulizer NE-C28	371	(33.6)
	OMRON Compressor-type Nebulizer NE-C29	135	(12.2)
	OMRON Compressor-type Nebulizer NE-C30	54	(4.9)
	Soffio®	45	(4.1)
	VOYAGE®	132	(12)
	InnoSpire Mini® Compressor	44	(4.0)
	Millicon®-Pro	45	(4.1)
	Millicon®-Cube	42	(3.8)
	Other [d]	106	(9.6)

[a] Break down of age (in months): 2 months of age: 2 patients, 3 months of age: 1 patient, 4 months of age: 7 patients, 5 months of age: 4 patients, 6 months of age: 14 patients, 7 months of age: 14 patients, 8 months of age: 13 patients, 9 months of age: 8 patients, 10 months of age: 11 patients, 11 months of age: 13 patients.
[b] The extent of influenza symptoms (nasal symptoms and cough) at initial visit was scored as "None: 0 pts," "Mild: 1 pt," "Moderate: 2 pts," and "Severe: 3 pts.
[c] Inhalation of laninamivir was discontinued at 1 min. The investigator judged the daily dosage to be 20 mg.
[d] Break down of other models: OMRON Compressor-type Nebulizer NE-C16: 17 patients, OMRON Ultrasonic Nebulizer NE-U780: 13 patients, Nescojet® AZ-11: 11 patients, OMRON Ultrasonic Nebulizer NE-U17: 10 patients, OMRON Compressor-type Inhaler NE-C11: 10 patients, MMI Compressor-type Nebulizer AQUA-Neb: 8 patients, Nisshou-type Compressor for Inhalation: 6 patients, SEPA®: 5 patients, VIGOR mist Lite®: 5 patients, OMRON Compressor-type Nebulizer NE-C13: 4 patients, Millicon®-S: 4 patients, PARI MASTER®: 4 patients, EUROSOL®: 3 patients, SEPA®-II: 2 patients, TAIYU Nebulizer moter: 2 patients, PARI boy®: 1 patient, MEDIC-AID PROTA-NEB: 1 patient.

No. 171, dated December 20, 2004).

2. Patients and methods

2.1. Patients

Subjects were pediatric 0–4 year old patients who were judged to be infected with the influenza A or B virus by a rapid influenza diagnostic kit and administered laninamivir for the first time from November 2019 to April 2020. Written informed consent to participation in this surveillance was obtained from a legal representative of the patient (e.g. a guardian).

2.2. Study drug

Laninamivir (brand name: Inavir for Inhalation Suspension Set) was used as the study drug. Laninamivir was administered using the dosage and administration method as directed by the package insert.

2.3. Surveillance procedures

Subjects were enrolled by the centralized enrollment system. The investigators entered the required information on the patient enrollment form within 7 days after inhalation of the study drug and faxed it to the enrollment center. They asked the legal representative of a subject (e.g. a guardian) to record the following information in a "patient diary" and to mail or bring it to them:

· Did any unfavorable symptoms newly develop within 15 days of inhalation of the study drug?
If any unfavorable symptoms newly developed, the legal representative should contact the investigator with the details.
· The legal representative should measure and record the patient's temperature twice a day, once each in the morning and afternoon for 15 days.

2.4. Attributes investigated

For the investigated patient characteristics, refer to the attributes in Table 1. In addition, the date and time of the onset of influenza are included as for patient attributes. Concomitant medications, clinical examinations and adverse events are included.

2.5. Safety and efficacy criteria

Medically untoward events emerging following administration of laninamivir were defined as adverse events (AEs). AEs that were clearly or likely to be causally related to the study drug were defined as adverse drug reactions (ADRs).

Efficacy was evaluated by time to fever resolution, defined as "(the date and time when the temperature first fell 37.4 °C or lower) (the date and time when the study drug was administered)". If the date and time of fever resolution was unknown or missing, it was defined as time until the date and time when the last temperature was measured in the patient diary, which was handled as discontinuation in the analysis.

Patients who were suspected of having an infection with a viral or bacterial pathogen other than the influenza virus and patients with a temperature lower than 38.0 °C at initial visit were excluded from evaluation of efficacy.

2.6. Statistical analysis

To determine risk factors associated with the occurrence of ADRs, Fisher's exact test were performed. With regard to the time to fever resolution, the median values were calculated using Kaplan-Meier method. To determine factors associated with the time to fever resolution, Cox proportional hazards model by virus type were performed. Patients with any missing data were excluded from data analysis. The level of significance was set at $P<5\%$ two-sided. All of the various data analyses were performed with SAS System Release 9.4 (SAS Institute Inc, Cary, NC, USA).

Table 2
Incidence of ADRs (patients evaluated for safety)

	Studies before approval [a]		Post-marketing surveillance	
Number of study sites	105		206	
Number of patients studied	441		1104	
Number of patients with ADRs	9		11	
Number of ADRs	12		15	
Percentage of patients with ADRs (%)	2.04		1	
Type of ADRs [b]	Incidence of ADRs [n (%)] [c]			
Psychiatric disorders	-	-	3	(0.27)
Delirium	-	-	1	(0.09)
Hallucination	-	-	2	(0.18)
Inappropriate affect	-	-	1	(0.09)
Restlessness	-	-	1	(0.09)
Nervous system disorders	1	(0.22)	4	(0.36)
Depressed level of consciousness	-	-	1	(0.09)
Febrile convulsion	-	-	1	(0.09)
Convulsive attack	-	-	2	(0.18)
Hypoaesthesia	1	(0.22)	-	-
Gastrointestinal disorders	6	(1.36)	2	(0.18)
Diarrhea	2	(0.45)	1	(0.09)
Vomiting	2	(0.45)	1	(0.09)
Colitis ischaemic	1	(0.22)	-	-
Constipation	1	(0.22)	-	-
Nausea	1	(0.22)	-	-
Musculoskeletal and connective tissue disorders	-	-	1	(0.09)
Muscular weakness	-	-	1	(0.09)
Pain in extremity	-	-	1	(0.09)
General disorders and administration site conditions	-	-	2	(0.18)
Fever	-	-	1	(0.09)
Screaming	-	-	1	(0.09)
Laboratory tests	2	(0.45)	-	-
Alanine aminotransferase increased	1	(0.22)	-	-
Aspartate aminotransferase increased	1	(0.22)	-	-
Blood lactate dehydrogenase increased	1	(0.22)	-	-
Liver function tests increased	1	(0.22)	-	-

[a] Trials: J310: a clinical trial in subjects the age of 10 and over, J311: a clinical trial in subjects under the age of 10
[b] Numbers were tallied in accordance with the terminology in the ICH Medical Dictionary for Regulatory Activities/J (MedDRA/J Version 23.0)
[c] The incidence rate of ADRs was calculated as (number of patients experiencing any ADR/number of patients evaluated for safety) ×100 (%).

3. Results

3.1. Surveillance population

In this surveillance, 1156 patients were enrolled at 208 facilities nationwide. Excluding 52 patients (a survey form not retrieved; 1, whether or not AE had occurred unknown; 51), safety was evaluated in 1104 patients.

Of the 1104 patients, excluding 223 patients (a temperature lower than 38.0 °C at initial visit: 172, infected with other viral or bacterial pathogen:11, no use of a jet nebulizer:18, "unknown" time to fever resolution:22), efficacy was evaluated in 881 patients.

No patients withdrew their consent to participate in this surveillance.

3.2. Baseline patient characteristics

Characteristics of the 1104 patients who were evaluated for safety are shown in Table 1.

Seven-point-nine percent of patients (87 patients) were age 0, 16.8% (185 patients) were age 1, 17.3% (191 patients) were age 2, 26.4% (291 patients) were age 3, and 31.7% (350 patients) were age 4. The mean temperature at initial visit was 38.7 ± 0.8 °C. Results of influenza virus kits indicated that 88.9% of patients were type A, 10.7% were type B, and 0.4% were mixed type. The scores for influenza symptoms at initial visit was 2.4 ± 1.3 points, and 33.1% of patients "had" a history of influenza vaccination. Five-point-three percent of patients "had" a history of febrile convulsion. Of 11.9% of patients who "had" a history of allergies, 2.2% had an allergy to dairy products. Among the patients with underlying diseases/complications or high-risk underlying disease, 0.1% (1 patient) had liver dysfunction and 4.1% (45 patients) had chronic respiratory disease, respectively.

4. Safety

4.1. Incidence and type of ADRs

The incidence of ADRs in this surveillance was 1.00% (11/1104 patients), with 15 cases (Table 2).

Major ADRs were nervous system disorders such as convulsive attack in 4 patients (0.36%) and psychiatric disorders such as hallucinations in 3 patients (0.27%). ADRs that could not be expected from the precautions in the package insert occurred in 5 patients (7 cases): 2 cases of convulsive attack, each 1 case of febrile convulsion, fever, muscular weakness, a depressed level of consciousness, and pain in extremities. Serious ADRs were noted in 3 patients (5 cases): 2 cases of convulsive attack, each 1 case of muscular weakness, a depressed level of consciousness, pain in extremities. Excluding 2 patients with unknown outcome, all patients recovered or their symptoms were alleviated. One

Table 3
Risk factors for the occurrence of ADRs (patients evaluated for safety).

Risk factors	Categories	Number of patients	Number of patients with ADRs (%)		Fisher's exact probability test
Age (years)	0	87	0	(0.00)	P=0.4823
	1	185	3	(1.62)	
	2	191	3	(1.57)	
	3	291	1	(0.34)	
	4	350	4	(1.14)	
Sex	Male	564	6	(1.06)	P>0.9999
	Female	540	5	(0.93)	
Testing with a rapid diagnosis kit of influenza virus type	Influenza A	982	11	(1.12)	P=0.6340
	Influenza B	118	0	(0.00)	
	Mixed type	4	0	(0.00)	
Body temperature at initial visit	<37.5°C	73	0	(0.00)	P=0.8602
	37.5°C≦ <38.0°C	101	0	(0.00)	
	38.0°C≦ <38.5°C	237	3	(1.27)	
	38.5°C≦	693	8	(1.15)	
Total influenza symptoms score at initial visit[a]	≦3 pts	864	10	(1.16)	P=0.4729
	4 pts≦	240	1	(0.42)	
Vaccination against influenza (after September 2019)	No	623	6	(0.96)	P>0.9999
	Yes	365	4	(1.10)	
History of febrile convulsion	No	1020	10	(0.98)	P=0.4573
	Yes	58	1	(1.72)	
History of allergies	No	918	9	(0.98)	P=0.6369
	Yes	131	2	(1.59)	
Allergy to dairy products	No	1012	11	(1.09)	P>0.9999
	Yes	24	0	(0.00)	
Underlying disease/complication	No	989	11	(1.11)	P=0.6164
	Yes	114	0	(0.00)	
High-risk underlying disease	No	1058	11	(1.04)	P>0.9999
	Yes	45	0	(0.00)	
Time from the onset of influenza to inhalation of laninamivir	≦12 h	393	5	(1.27)	P=0.5056
	12 h< ≦24 h	464	4	(0.86)	
	24 h< ≦36 h	135	0	(0.00)	
	36 h< ≦48 h	48	1	(2.08)	
	48 h<	30	0	(0.00)	
Dosage of laninamivir	160mg	1103	11	(1.00)	P>0.9999
	20mg[b]	1	0	(0.00)	
Inhalation time	≦8 min	237	3	(1.27)	P=0.6232
	8 min< ≦10 min	537	4	(0.74)	
	10 min<	314	4	(1.27)	

(*continued on next page*)

Table 3 (*continued*)

Risk factors	Categories	Number of patients	Number of patients with ADRs (%)		Fisher's exact probability test
Model of compressor used	Recommended				
	PARI boy® SX	130	2	(1.54)	P=0.6949
	PARI YPSITA®	0	0	(-)	
	OMRON Compressor-type Nebulizer NE-C28	371	3	(0.81)	
	OMRON Compressor-type Nebulizer NE-C29	135	2	(1.48)	
	OMRON Compressor-type Nebulizer NE-C30	54	0	(0.00)	
	Soffio®	45	0	(0.00)	
	VOYAGE®	132	3	(2.27)	
	InnoSpire Mini® Compressor	44	0	(0.00)	
	Millicon®-Pro	45	0	(0.00)	
	Millicon®-Cube	42	1	(2.38)	
	Other[c]	106	0	(0.00)	
Concomitant medications	No	238	3	(1.26)	P=0.7114
	Yes	866	8	(0.92)	

[a] The extent of influenza symptoms (nasal symptoms and cough) at initial visit was scored as "None: 0 pts," "Mild: 1 pt," "Moderate: 2 pts," and "Severe: 3 pts.

[b] Inhalation of the study drug was discontinued at 1 min. The investigator judged the daily dose to be 20 mg.

[c] Break down of other models: OMRON Compressor-type Nebulizer NE-C16: 17 patients, OMRON Ultrasonic Nebulizer NE-U780: 13 patients, Nescojet® AZ-11: 11 patients, OMRON Ultrasonic Nebulizer NE-U17: 10 patients, OMRON Compressor-type Inhaler NE-C11: 10 patients, MMI Compressor-type Nebulizer AQUA-Neb: 8 patients, Nisshou-type Compressor for Inhalation: 6 patients, SEPA®: 5 patients, VIGOR mist Lite®: 5 patients, OMRON Compressor-type Nebulizer NE-C13: 4 patients, Millicon®-S: 4 patients, PARI MASTER®: 4 patients, EUROSOL®: 3 patients, SEPA®-II: 2 patients, TAIYU Nebulizer moter: 2 patients, PARI boy®: 1 patient, MEDIC-AID PROTA-NEB: 1 patient.

patient with unknown outcome developed convulsive attack (serious) on the day of drug inhalation. It was reported that the patient was admitted to another hospital on the same day with no details, and the patient did not return for a visit. The other patient developed a fever (non-serious) on day 5 after inhalation of the study drug did not return for a visit.

4.2. Onset time and duration of ADRs

The time of onset and duration of the 15 ADRs were examined.

The time of onset of ADRs was on day 1 (the day of the study drug inhalation) in 40.00%, day 2 in 20.00%, day 3 in 26.67%, day 4 in 6.67%, and day 5 in 6.67%. Eighty-six-point-six-seven percent of the ADRs occurred by day 3. The ADRs which occurred the latest was a case of "fever," on day 5. The investigator remarked that "this was presumably a biphasic fever from influenza, but the patient may also have not responded adequately to laninamivir."

The duration of ADRs (excluding a total of 2 cases: "seizures" and of "fever" in which the outcome was unknown) was 1 day in 7.69%, 2 days in 23.08%, 3 days in 38.46%, 4 days in 7.69%, and 6 days in 23.08%. Sixty-nine-point-two-three percent of ADRs disappeared or were alleviated within 3 days. ADRs of the longest duration were 3 cases of "a depressed level of consciousness," "muscular weakness," and "pain in extremities" (occurring in the same patient). These occurred on day 3 and lasted for 6 days to recover with administration of an intravenous drip.

4.3. Risk factors for the occurrence of ADRs

As for factors affecting incidence of ADRs, 16 attributes were examined by Fisher's exact probability test. No factors were found to significantly affect the incidence of ADRs (Table 3).

5. Efficacy

5.1. Duration to fever resolution stratified by influenza virus type

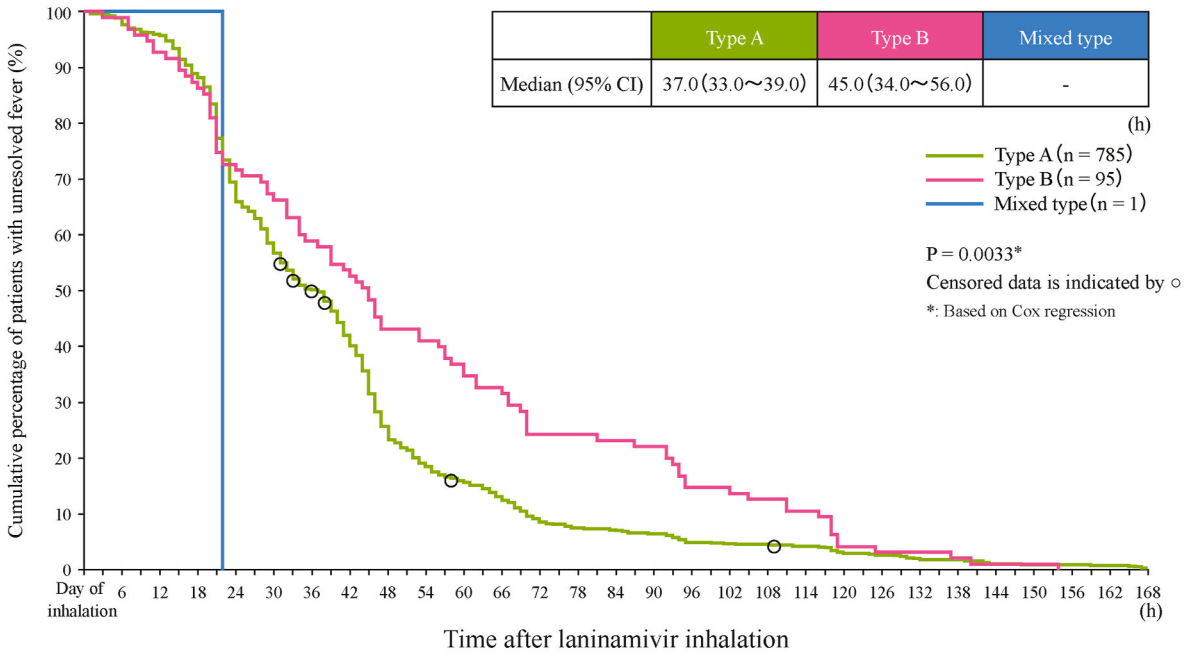
The time to fever resolution by influenza virus types is shown in Fig. 1. The median time to fever resolution was 37.0 h for type A virus, 45.0 h for type B virus, and 22.0 h for mixed type (1 patient only, aged 4) with significant difference (P = 0.0033). In 91.4% patients infected with type A virus and in 75.8% patients infected with type B virus, fever resolved within 72 h of laninamivir inhalation.

5.2. Duration to fever resolution stratified by age

The time to fever resolution by virus type stratified by age is shown in Fig. 2. The median time to fever resolution for type A virus ranged 29.5–41.0 h, with significant differences between the age groups (P = 0.0022). The time for the age of 2 was the longest. In all age groups, fever resolved in 85% or more patients within 72 h of laninamivir inhalation. The median time to fever resolution for type B virus ranged 39.0 to 46.0, with no significant differences between the age groups (P = 0.7047). Fever resolved in 70% or more patients in the all age groups within 72 h.

5.3. Duration to fever resolution stratified by presence of high-risk conditions

The time to fever resolution stratified by whether or not the patient was high-risk is shown in Fig. 3. The median time to fever resolution for type A virus was 42.0 h for high-risk patients and 35.0 h for non-high-risk patients, with no significant difference (P = 0.0932). For type B virus, only 1 patient was high-risk (time to fever resolution: 53.0 h); therefore, effects on the time to fever resolution could not be evaluated. For non-high-risk patients infected with type B virus, the median time to fever resolution was 44.5 h.



Cumulative percentage of patients with resolved fever (%)

Time to fever resolution (h)	6	9	12	15	18	21	24	36	48	72	96	120	144	168
Type A	2.4	3.7	4.3	8.5	11.8	22.7	34.1	49.8	76.7	91.4	95.1	97.1	98.9	99.6
Type B	1.1	4.2	7.4	10.5	13.7	25.3	28.4	41.1	56.8	75.8	85.3	95.8	98.9	100.0
Mixed type	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Fig. 1. Time to fever resolution by virus type. No legend.

5.4. Relationship between the model of compressor and the time to fever resolution

Twenty-three models of jet nebulizers (9 recommended, 14 others) were used when inhaling laninamivir (Fig. 4).

About 90% patients used the recommended models. Regardless of compressor models, the median inhalation time was approximately 10 min.

The median time to fever resolution in patients of type A virus was 22.0–41.0 h for patients using the recommended models and 38.5 h for patients using "others" (Fig. 5). No significant difference in the time to fever resolution between the models were noted (P = 0.4012). In the case of patients infected with the influenza B (Fig. 6), the median time to fever resolution was 39.0–79.5 h for patients using the recommended models and 21.0 h for patients using "others." No significant difference in the time to fever resolution between the models were noted (P = 0.4013).

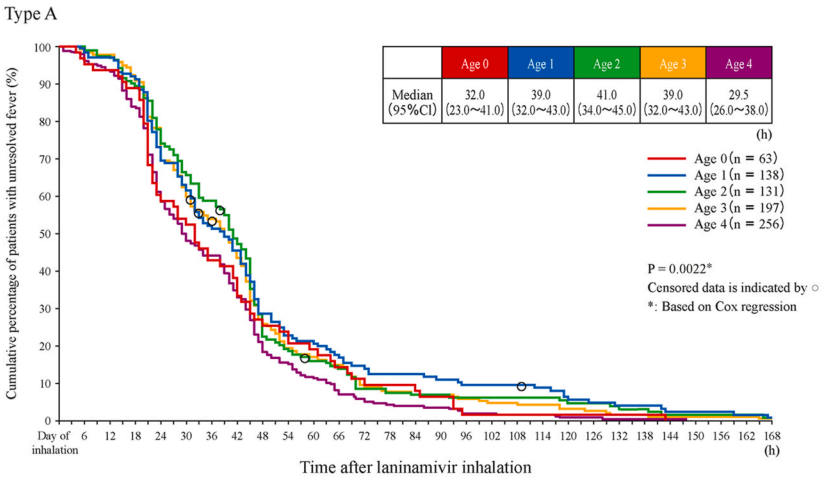
6. Discussion

Large-scale post-marketing surveillance of an inhaled powder with laninamivir has been conducted by Kashiwagi et al. [7]. The authors reported that only 1.1% patients under the age of 5 (42/3524 patients) received laninamivir, and that more detailed instruction for administration is important for young patients. The Japan Pediatric Society recommends oseltamivir and peramivir as the 2 anti-influenza drugs useable for children under the age of 5 but also cites the need to monitor trends in viral drug resistance [6]. Ikematsu et al. have assessed the susceptibility to NA inhibitors in the viruses epidemic for 7 continuous seasons since the 2010-11 season, and reported there was no resistant virus to laninamivir [8]. Given this context, Daiichi Sankyo Co., Ltd. launched a preparation that could be administered to patients under the age of 5 via a nebulizer (brand name: Inavir for Inhalation Suspension Set) in October 2019. The preparation has undergone the 2 clinical trials for development: J310 trial for the age of 10 and over, and J311 trial for the age of under 10. Subjects under the age of 5 were 71 in those trials [9].

To comprehend early the safety and efficacy of the drug in children under the age of 5, who are likely to often use it, we conducted the post-marketing surveillance with a target sample size of 1000.

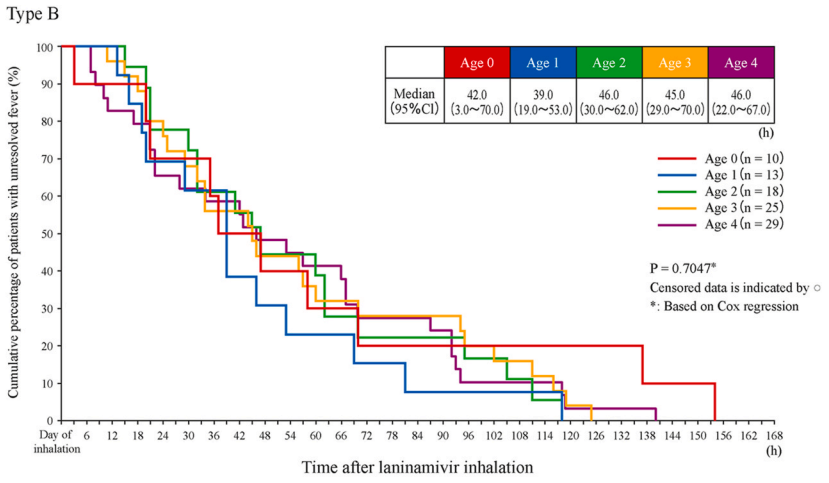
There was no increase in the incidence of ADRs in this surveillance (1.00%), compared to that in the clinical trials for development (2.04%). Regarding ADRs that could not be expected from the precautions in the package insert, the investigator remarked that the 2 cases of convulsive attack and 1 case of febrile convulsion "could be affected by influenza infection due to their onset with a fever." Katayose et al. reported that febrile convulsion was observed in about 6% children under the age of 6 with influenza [10]. The frequency of convulsive attack and febrile convulsion in our surveillance (0.27%), does not seem to pose a problem clinically. A fever "might be a biphasic fever associated with influenza or showed an inadequate effect of laninamivir." Serious ADRs were noted in 3 patients (5 cases), among them the depressed level of consciousness, muscular weakness, and pain in extremities were noted in the same patient. The investigator remarked that "they presumably might be due to influenza." The most frequent onset of ADRs and duration time of ADRs in this surveillance were similar to those of post-marketing surveillance of Inavir Dry Powder Inhaler conducted in the all age groups [11]. Therefore, the study drug was confirmed to be unlikely to cause delayed ADRs or to prolong ADRs in the age under 5. Sixteen factors that potentially affected occurrence of the ADRs were examined, and none of them were found to be significant risk factors.

The results of current surveillance verified that the study drug can be safely administered to patients in the age under 5 (the youngest surveyed; 2 months), and to patients with chronic respiratory diseases (a



Cumulative percentage of patients with resolved fever (%)

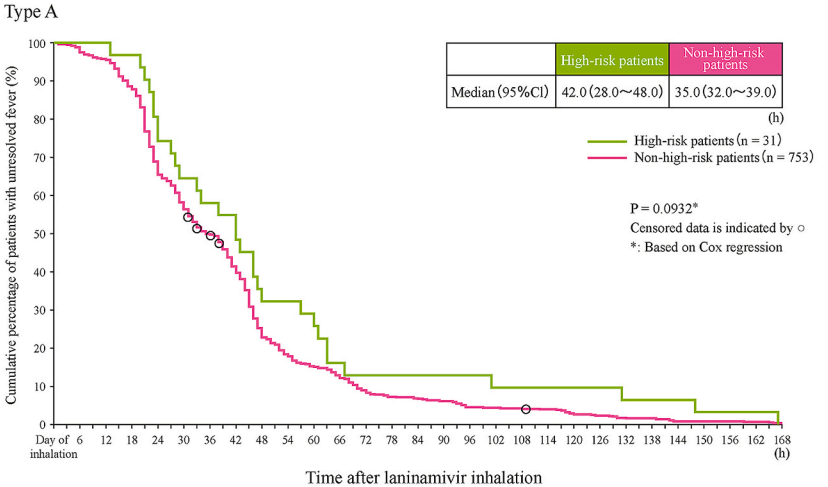
Time to fever resolution (h)	6	9	12	15	18	21	24	36	48	72	96	120	144	168
Age 0	4.8	6.3	6.3	9.5	11.1	31.7	41.3	57.1	74.6	90.5	98.4	98.4	100.0	100.0
Age 1	1.4	2.9	2.9	7.2	8.7	18.8	30.4	48.6	71.4	86.1	90.5	94.4	97.6	99.2
Age 2	1.5	2.3	2.3	8.4	10.7	14.5	26.0	41.2	77.6	91.5	93.8	95.4	98.5	99.2
Age 3	1.0	2.5	3.0	5.1	9.1	19.8	30.5	46.2	74.1	90.9	94.1	96.8	98.9	99.5
Age 4	3.9	5.1	6.6	11.7	16.4	28.9	41.4	55.9	81.6	94.9	98.0	99.2	99.6	100.0



Cumulative percentage of patients with resolved fever (%)

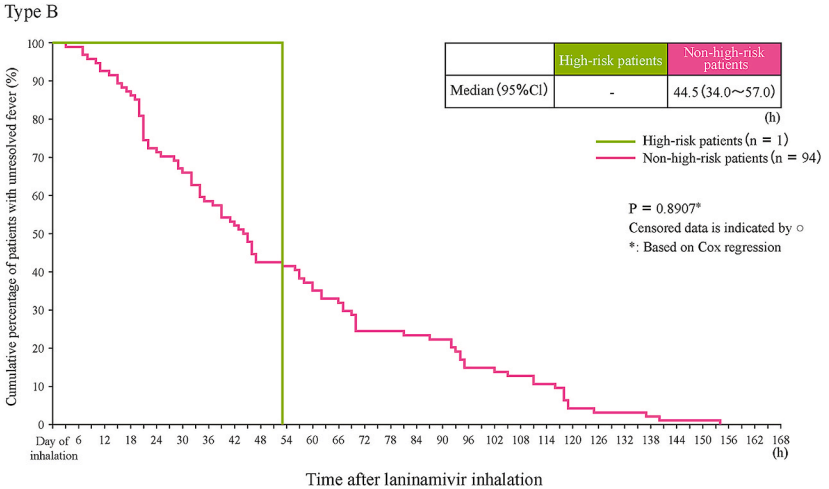
Time to fever resolution (h)	6	9	12	15	18	21	24	36	48	72	96	120	144	168
Age 0	10.0	10.0	10.0	10.0	10.0	30.0	30.0	40.0	60.0	80.0	80.0	80.0	90.0	100.0
Age 1	0.0	0.0	0.0	7.7	15.4	30.8	30.8	38.5	69.2	84.6	92.3	100.0	100.0	100.0
Age 2	0.0	0.0	0.0	5.6	5.6	22.2	22.2	38.9	55.6	77.8	83.3	100.0	100.0	100.0
Age 3	0.0	0.0	4.0	8.0	12.0	20.0	24.0	44.0	56.0	72.0	80.0	96.0	100.0	100.0
Age 4	0.0	10.3	17.2	17.2	20.7	27.6	34.5	41.4	51.7	72.4	89.7	96.6	100.0	100.0

Fig. 2. Time to fever resolution by age. No legend.



Cumulative percentage of patients with resolved fever (%)

Time to fever resolution (h)	6	9	12	15	18	21	24	36	48	72	96	120	144	168
with high-risk underlying disease	0.0	0.0	0.0	3.2	3.2	9.7	25.8	41.9	67.7	87.1	87.1	90.3	93.5	100.0
without high-risk underlying disease	2.5	3.9	4.5	8.8	12.2	23.2	34.5	50.2	77.2	91.7	95.4	97.4	99.2	99.6



Cumulative percentage of patients with resolved fever (%)

	6	9	12	15	18	21	24	36	48	72	96	120	144	168
High-risk patients	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	100.0	100.0
Non-high-risk patients	1.1	4.3	7.4	10.6	13.8	25.5	28.7	41.5	57.4	75.5	85.1	95.7	98.9	100.0

Fig. 3. Time to fever resolution by the patient with high-risk underlying disease. No legend.

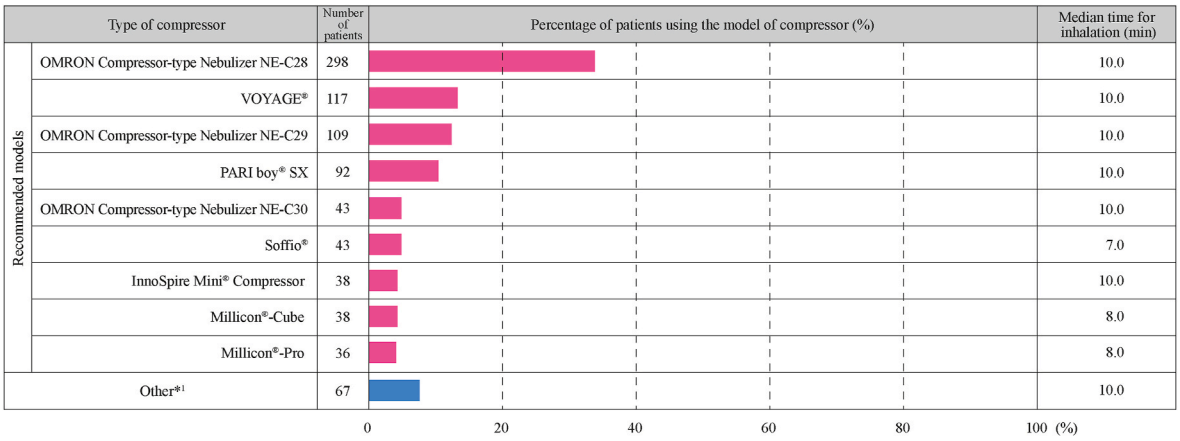
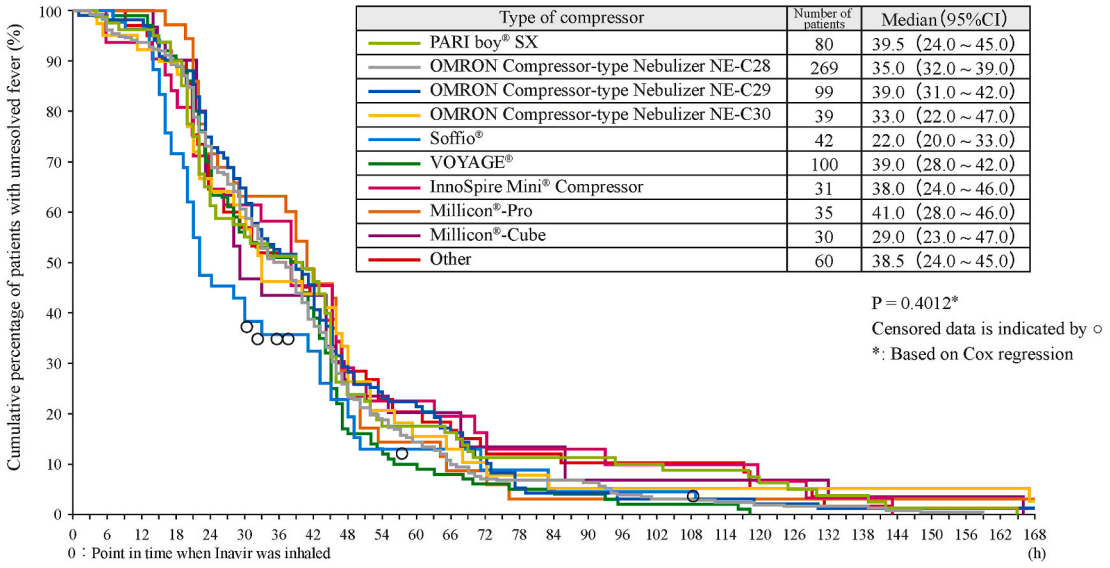


Fig. 4. Inhalation time of laninamivir by each model of compressor*1 OMRON Compressor-type Nebulizer NE-C16: 11 patients, OMRON Compressor-type Inhaler NE-C11: 10 patients, MMI Compressor-type Nebulizer AQUA-Neb: 7 patients, Nescojet® AZ-11: 7 patients, VIGOR mist Lite®: 5 patients, SEPA®: 5 patients, Nisshou-type Compressor for Inhalation: 5 patients, OMRON Compressor-type Nebulizer NE-C13: 4 patients, PARI MASTER®: 4 patients, Millicon®-S: 3 patients, EUROSOL®: 3 patients, SEPA®-II: 1 patient, TAIYU Nebulizer moter: 1 patient, PARI boy®: 1 patient. The atomizing performance of "nebulizer parts accompanying the study drug" combined with "other compressors" was not verified.

high-risk factor) without major problems. In addition, due to modification of excipients, no ADRs were noted in children with allergy to dairy products.

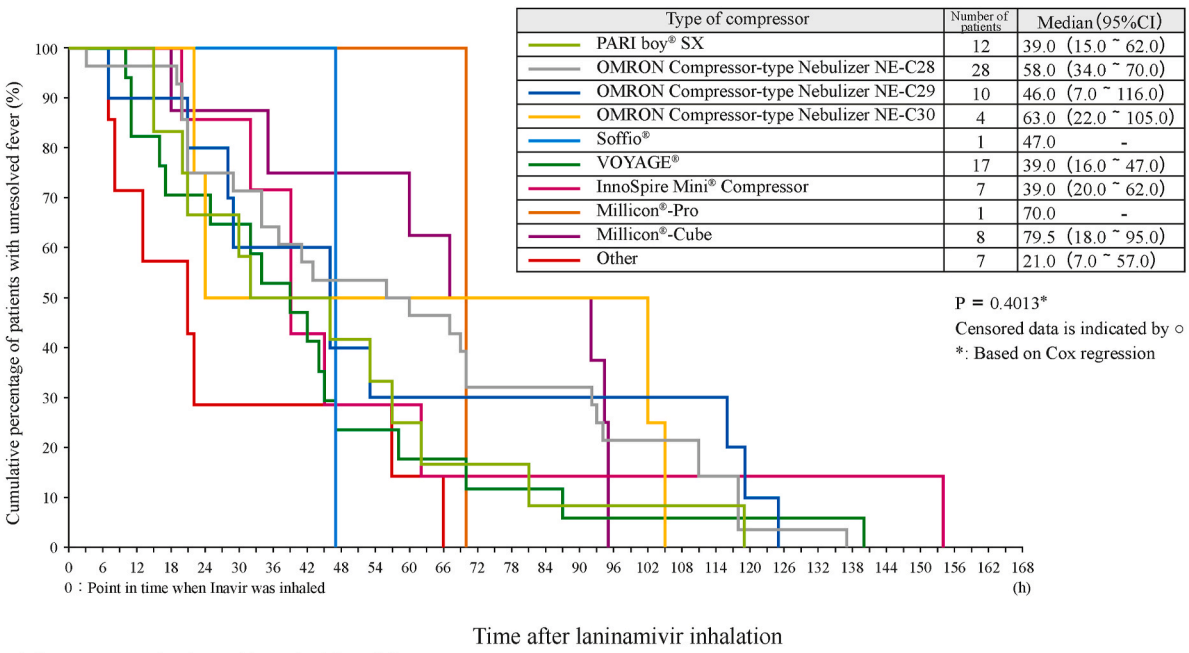
Efficacy of the study drug was examined with time to fever resolution. The median time by virus type was 37.0 h for type A virus (785 patients), 45.0 h for type B virus (95 patients), and 22.0 h (1 patient only) for mixed type, with significant difference. The geometric mean of IC_{50} values of laninamivir during the 7 seasons since the 2010–2011 season was 1.37–2.15 nM for A(H1N1) pdm, 2.72–4.69 nM for A(H3N2), and 11.9–21.4 nM for the influenza B virus. NA inhibition activity of laninamivir for type A virus was found to be 5–10 times higher than that for type B virus [12]. In addition, other NA inhibitors tended to result in a shorter time to fever resolution in patients infected with type A virus than in patients infected with type B virus, presumably indicating a



Cumulative percentage of patients with resolved fever (%)

Type of compressor (h)	6	9	12	15	18	21	24	36	48	72	96	120	144	168
PARI boy® SX	2.5	3.8	3.8	6.3	10.0	25.0	38.8	48.8	76.3	88.8	90.0	93.8	98.8	100.0
OMRON Compressor-type Nebulizer NE-C28	4.1	5.6	6.7	9.3	11.5	21.2	31.2	50.2	77.0	92.9	96.3	98.1	99.3	100.0
OMRON Compressor-type Nebulizer NE-C29	2.0	2.0	3.0	8.1	11.1	17.2	27.3	48.5	73.7	89.9	97.0	98.0	99.0	99.0
OMRON Compressor-type Nebulizer NE-C30	5.1	5.1	7.7	10.3	12.8	28.2	35.9	53.8	71.8	92.3	94.9	94.9	94.9	97.4
Soffio®	0.0	4.8	4.8	16.7	28.6	45.2	54.8	64.4	80.6	91.4	95.7	95.7	95.7	95.7
VOYAGE®	0.0	1.0	1.0	8.0	10.0	20.0	35.0	49.0	84.0	94.0	98.0	100.0	100.0	100.0
InnoSpire Mini® Compressor	6.5	6.5	6.5	9.7	19.4	29.0	35.5	41.9	71.0	87.1	90.3	93.5	100.0	100.0
Millicon®-Pro	0.0	0.0	0.0	0.0	2.9	14.3	28.6	37.1	77.1	94.3	97.1	97.1	97.1	97.1
Millicon®-Cube	0.0	0.0	0.0	6.7	10.0	16.7	36.7	56.7	76.7	86.7	93.3	93.3	96.7	100.0
Other	0.0	3.3	3.3	8.3	10.0	25.0	36.7	48.3	71.7	88.3	90.0	95.0	100.0	100.0

Fig. 5. Time to fever resolution of type A by model of compressor. No legend.



Cumulative percentage of patients with resolved fever (%)

Type of compressor (h)	6	9	12	15	18	21	24	36	48	72	96	120	144	168
PARI boy® SX	0.0	0.0	0.0	16.7	16.7	33.3	33.3	50.0	58.3	83.3	91.7	100.0	100.0	100.0
OMRON Compressor-type Nebulizer NE-C28	3.6	3.6	3.6	3.6	3.6	25.0	25.0	35.7	46.4	67.9	78.6	96.4	100.0	100.0
OMRON Compressor-type Nebulizer NE-C29	0.0	10.0	10.0	10.0	10.0	20.0	20.0	40.0	60.0	70.0	70.0	90.0	100.0	100.0
OMRON Compressor-type Nebulizer NE-C30	0.0	0.0	0.0	0.0	0.0	0.0	50.0	50.0	50.0	50.0	50.0	100.0	100.0	100.0
Soffio®	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	100.0	100.0	100.0
VOYAGE®	0.0	0.0	17.6	17.6	29.4	29.4	29.4	47.1	76.5	88.2	94.1	94.1	100.0	100.0
InnoSpire Mini® Compressor	0.0	0.0	0.0	0.0	0.0	14.3	14.3	28.6	71.4	85.7	85.7	85.7	85.7	100.0
Millicon®-Pro	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0	100.0	100.0	100.0	100.0
Millicon®-Cube	0.0	0.0	0.0	0.0	12.5	12.5	12.5	25.0	25.0	50.0	100.0	100.0	100.0	100.0
Other	0.0	28.6	28.6	42.9	42.9	57.1	71.4	71.4	71.4	100.0	100.0	100.0	100.0	100.0

Fig. 6. Time to fever resolution of type B by model of compressor. No legend.

general trend for NA inhibitors [12–14].

While the number of type B-infected patients is limited to 95 in the current surveillance, as the median time to fever resolution in J311 trial in subjects under the age of 10 was 31.0 h for type A virus and 50.7 h for type B virus, there are presumably no clinical problems with efficacy of the study drug against type A virus and type B virus.

In the current surveillance, there was a significant difference among the median time to fever resolution in stratified ages (0, 1, 2, 3, 4), with no constant trends between age and the resolution time. Time to fever resolution in the age of 2 was slightly longer than that in other age groups, however, it was comparable to that of the same age in J311 trial, suggesting the study drug is not considered to pose a major problem clinically in the age of under 5.

This surveillance suggested that a nebulizer is a useful way to inhale the study drug for patients with a respiratory disease (e.g. bronchial asthma or chronic obstructive pulmonary disease). A jet type nebulizer needs be used to inhale laninamivir. During the clinical trials for development, PARI Boy SX was used uniformly. After marketing, medical facilities were given information on the 10 models of compressors that were recommended. Among them, 9 models were used in this surveillance, and all were shown to be available without any clinically significant difference in inhalation time.

From the above, there were no problems with the safety and efficacy of Inavir for Inhalation Suspension Set in children under the age of 5 using Jet type nebulizer. In terms of more convenience and improved compliance of taking the medicine, the study drug was suggested to be a useful agent to treat an infection with the influenza A or B virus.

Icmje statement

Takashi Nakano (A) was responsible for the organization and coordination of this surveillance from medical point of view. Yomei Matsuoka (B) was responsible for the organization and coordination of this surveillance. Kazuhito Shiosakai (C) was responsible for the data analysis. A, B, C, Hiroki Yamaguchi (D), Shuichi Chikada (E) and Toshihiro Chiba (F) developed the surveillance design. E was responsible for management of this surveillance, and D and F contributed to administration of this surveillance. D was responsible for the writing of this manuscript, and the orders contributed to the writing of this manuscript.

Declaration of competing interest

This investigation was sponsored by Daiichi Sankyo Co., Ltd.

T. Nakano has previously received honoraria from Daiichi Sankyo Co., Ltd for medical advice. H. Yamaguchi, T. Chiba, K. Shiosakai, S. Chikada, and Y. Matsuoka are employees of Daiichi Sankyo Co., Ltd.

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