Inhaled Laninamivir Octanoate as Prophylaxis for Influenza in Children

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abstract

BACKGROUND: A single 20-mg dose of inhaled laninamivir octanoate is an effective treatment of influenza. However, the efficacy of laninamivir octanoate for the prevention of influenza in children <10 years of age has not yet been established.

METHODS: We conducted a double-blind, multicenter, randomized, placebo-controlled study to determine whether the efficacy of a single 20-mg dose of inhaled laninamivir octanoate to prevent the development of influenza was superior to that of placebo as prophylaxis for influenza in pediatric (<10 years) household members of index cases. Eligible subjects without influenza, in contact with an influenza-infected index case living in the same household, were blindly randomly assigned in a 1:1 ratio to receive 20 mg of laninamivir octanoate or placebo. The primary end point was the proportion of subjects who developed clinical influenza during a 10-day period.

RESULTS: A total of 343 subjects were randomly assigned, with 341 subjects included in the full analysis set for the primary analysis. The proportions of subjects who developed clinical influenza were 11% (18/171) in the laninamivir octanoate group and 19% (33/170) in the placebo group ($P = .02$). The relative risk reduction was 45.8% (95% confidence interval, 7.5% to 68.2%). The incidence of adverse events was similar in both groups.

CONCLUSIONS: A single 20-mg dose of inhaled laninamivir octanoate was effective and well tolerated as prophylaxis for influenza.

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WHAT'S KNOWN ON THIS SUBJECT: Neuraminidase inhibitors (NAIs) are recommended for chemoprophylaxis of influenza. But only a few clinical data are available on the prophylactic efficacy of NAIs in children <10 years of age.

WHAT THIS STUDY ADDS: This study demonstrates the efficacy of laninamivir as prophylaxis for influenza in children aged ≥2 and <10 years with a single 20-mg dose of inhaled laninamivir octanoate.

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Influenza is a common viral respiratory illness that could increase risks of hospitalization, severe morbidity, and death[1–3] in young children, elderly, and others with underlying medical conditions. Additionally, abnormal behavior in children has been reported in patients with influenza.[4–6] It is highly important to take preventive measures against seasonal influenza, particularly in the pediatric population. Prophylactic vaccination against influenza has been generally recommended for children, and vaccination rates among children had reached 40% to 60% during the 6 seasons of 2005/2006 to 2010/2011.[7] However, despite the increasing rates in influenza vaccination, an outbreak of 2009 pandemic influenza A (H1N1) [A(H1N1)pdm09] virus occurred, and oseltamivir-resistant strains emerged in the years after the pandemics.[8] Furthermore, during the 2013/2014 season in Japan, influenza A(H1N1) pdm09 virus cross-resistant to oseltamivir and peramivir was detected.[9] Such circumstances suggest the emergence and outbreak of new drug-resistant strains of influenza virus. Given the limitations of vaccination, extensive variations in the option for antiinfluenza prophylaxis are desirable as an adjunct to influenza vaccine.

Laninamivir potently inhibits neuraminidase activities of various influenza A and B viruses, including subtypes N1 to N9, influenza A(H1N1)pdm09 viruses, highly pathogenic avian influenza H5N1 viruses, and oseltamivir-resistant viruses.[10,11] The efficacy of a single 20-mg dose of laninamivir octanoate for influenza treatment in adults and children has been demonstrated.[12–15] In addition, the efficacy of a single 20-mg dose of laninamivir octanoate once daily for 2 days as postexposure prophylaxis of influenza in household members (adults and children ≥10 years of age) of index cases (first members of the household infected by influenza A or B virus in the 2011/2012 influenza season) has been demonstrated.[16]

However, the efficacy of laninamivir octanoate as prophylaxis for influenza in children <10 years of age has not yet been evaluated. We conducted a randomized controlled study to determine whether laninamivir octanoate is efficaciously superior compared with placebo, in pediatric (<10 years of age) household members of an index case as a prophylaxis of influenza.

METHODS

Study Design

This study was a randomized, double-blind, placebo-controlled trial conducted from November 2014 to March 2015 at 50 pediatric clinics in Japan. The study was approved by the ethics committee at each center and complied with the provisions of Good Clinical Practice and the Declaration of Helsinki.[17] All index cases, subjects, and their legally acceptable representatives provided written or oral informed consent in accordance with their age before enrollment in the study.[18]

Subjects

Eligible subjects were aged <10 years, had an axillary temperature of ≤36.9°C, had no influenzalike symptoms at the time of receiving consent, and were determined by the investigator of having sufficient inhalation capability for using an inhaler (evaluated by a test using training whistles[19]). Eligible index cases were the first members infected with influenza A or B virus in the 2014/2015 influenza season within the household, tested positive for influenza by the rapid diagnostic test. The study excluded subjects who were unable to start the treatment within 48 hours of the onset of influenza symptom in the index case, infected family members other than the index case was present within the household, had a history of abnormal behavior accompanied by influenza or pyrexia, hypersensitivity to neuraminidase inhibitors (NAIs), being treated with corticosteroid or other immunosuppressant, or had been treated with a NAI within 4 weeks before informed consent. Influenza inactivated-vaccine recipients in the 2014/2015 season were considered eligible because prophylaxis for influenza is particularly indicated for groups at risk for complications, and hence for whom influenza vaccination is recommended.

Study Procedure

Participants were blindly randomly assigned in a 1:1 ratio to receive 20 mg of inhaled laninamivir octanoate or placebo through an inhaler on day 1. The study used random allocation through an interactive Web response system that centrally assigned subjects on the basis of computer-generated permuted-block randomization by Bell Medical Solutions, Inc (Tokyo, Japan). Stratification factors for randomization were virus types for the index cases and influenza vaccination status of the 2014/2015 influenza season for the subjects. After confirming eligibility, the investigator enrolled the subjects through the Web system, which generated allocation numbers for the drug. The subjects, index cases, investigators, and trial personnel were blinded to the group assignment throughout the trial. If the subjects were deemed ineligible after obtaining informed consent, they were not enrolled. The investigator recorded whether subjects inhaled the drug well or not. The index cases were treated with oseltamivir or zanamivir. Participants were not allowed to use any other antiinfluenza agents before the diagnosis of influenza infection.

Clinical and Virological Monitoring

The legal representatives observed and recorded the axillary temperature and the presence or absence of any of the 7 influenza symptoms (headache, myalgia/arthralgia, fatigue, chills/sweats, nasal symptoms, sore throat, and cough) of subjects twice daily over a 10-day period on diary cards.

For viral detection, anterior nose and posterior pharyngeal throat swabs were taken from the index cases at the initial visit and from the subjects on days 1, 3, and 11. Samples were also taken from the subjects during an outpatient visit within 3 days if axillary temperature of ≥37.5°C or the onset of influenza symptoms were confirmed. If the subjects were diagnosed with influenza virus infection by a rapid diagnostic test at the visits, they were provided with appropriate treatment.

Viral isolation was performed by local laboratories for all samples collected in a tube.

Viral RNA was extracted from supernatant fluids using QIAamp viral RNA minikit (Qiagen, Inc, Hilden, Germany) and virus was confirmed by determining the virus type and subtype, based on a reverse transcription polymerase chain reaction[20] with specific primers designed from the hemagglutinin sequence of the influenza A(H1N1) pdm09, seasonal influenza A(H1N1), influenza A(H3N2), or influenza B viruses. All laboratory virological procedures were performed by LSI Medience Corporation (Tokyo, Japan).

Efficacy End Points

The primary efficacy end point, clinical influenza, was the proportion of subjects who developed clinical influenza, defined as laboratory-confirmed influenza with an axillary temperature of ≥37.5°C and ≥2 influenza symptoms present from days 1 through 11. The secondary end points included the proportions of subjects with symptomatic influenza (laboratory-confirmed influenza with either an axillary temperature of ≥37.5°C or ≥1 influenza symptom present), asymptomatic influenza (laboratory-confirmed influenza without an axillary temperature of ≥37.5°C and no influenza symptoms present), and influenza infection (laboratory-confirmed influenza, excluding participants with confirmed influenza virus at baseline).

Safety and Tolerability

For safety assessments, all adverse events were assessed to determine whether they corresponded to abnormal behavior on the basis of the definition of Ministry of Health, Labor, and Welfare,[21] regardless of infection. Blood and urine samples were taken on days 1 and 11 to perform hematology, blood chemistry, and urinalysis as part of safety evaluation.

Statistical Analyses

The primary population for evaluating efficacy was defined as the full analysis set (FAS). FAS in the current study is defined as a population excluding subjects in which the study drug has not been administered, from population on the basis of the intention-to-treat principle. Between-group comparisons were made by 2-sided Fisher's exact test with a significance level of 5%. For protective efficacy, relative risk reduction compared with placebo and the 95% confidence interval (CI) on the basis of normal approximation were estimated. Symptomatic influenza, asymptomatic influenza, and influenza infection were analyzed as the secondary end points in the same manner as for the primary end point. The safety analysis population included all subjects except for those who received no treatment or could not be investigated for safety after enrollment. All analyses were performed by using SAS System Release 9.2 (SAS Institute, Inc, Cary, NC). The planned sample size was 300 subjects on the basis of the assumptions that the relative risk reduction would be at least 70% and the proportion of subjects with clinical influenza in the placebo group would be 15% as in previous studies,[22,23] corresponding to a rate of 4.5% in the laninamivir octanoate group. We estimated that 150 subjects in each group would provide 80% power to detect superior efficacy.

RESULTS

Study Population

A total of 343 subjects were randomly assigned. Of these, 2 subjects were excluded from the analyses due to discontinuation before administration, because they were unable to start study treatment within 48 hours after the initial onset of influenza symptom in the index case. A total of 341 subjects were included in the FAS and were assigned to the laninamivir octanoate group (N = 171) and in the placebo group (N = 170; Fig 1).

The demographic characteristics of subjects and index cases were comparable in the FAS (Table 1). Most of the index cases were children ≤15 years of age (all cases were ≥2 years of age), and subjects were mostly siblings of the index case. Of all index cases, 333 (98%; 165 [97%] and 168 [99%] cases of household contacts in the laninamivir octanoate group and in the placebo group, respectively) were infected with influenza A(H3N2) virus. Among all subjects, 140 (41%) had received the 2014/2015 seasonal influenza vaccination (Table 1). All index cases were treated with either oseltamivir or zanamivir in the current study.

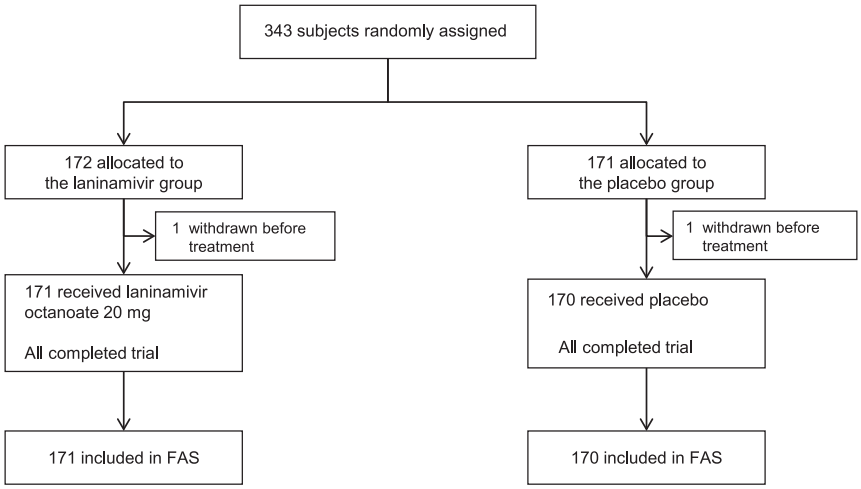

FIGURE 1
Subjects flowchart. A total of 341 subjects were included in the safety analysis set (171 subjects in the laninamivir group and 170 in the placebo group).

Efficacy Outcomes

In the FAS, the proportion of subjects with clinical influenza, the primary end point, were 11% (18/171) and 19% (33/170) in the laninamivir octanoate group and placebo group, respectively (Table 2; $P = .02$). The relative risk reduction was 45.8% (95% CI, 7.5% to 68.2%; Table 2). The proportion of subjects with symptomatic influenza was 15% (26/171) in the laninamivir octanoate group and 27% (45/170) in the placebo group ($P = .01$). The proportions of subjects with influenza infection in laninamivir octanoate group and placebo groups were 13% (20/153) and 30% (46/155), respectively, showing significant reduction in the incidence of infected cases ($P < .001$). The proportion of subjects with asymptomatic influenza appeared to be lower but was not significant (Table 2).

In the subpopulation of subjects who were the household members of index cases who had tested virus-positive at baseline (18/168 and 33/168 clinical influenza cases in laninamivir octanoate and placebo groups, respectively), the relative risk reduction was 45.5% (95% CI, 7.1% to 68.0%), and the relative risk reduced to 64.5% (95% CI, 26.7% to 82.8%) when that subpopulation only included subjects who were virus-negative at baseline (9/150 and 26/154 clinical influenza cases

TABLE 1 Demographic and Baseline Characteristics of Subjects (FAS) and Index Cases

Subjects (Household Contacts)			Index Cases[a]		
Characteristic	Laninamivir 20 mg	Placebo	Characteristic	Household Contacts, Laninamivir 20 mg	Household Contacts, Placebo
No.	*N* = 171	*N* = 170	No.	*N* = 171	*N* = 170
Age			Age		
Mean ± SD, y	6.7 ± 1.7	6.8 ± 1.7	Mean ± SD, year	8.9 ± 7.5	8.9 ± 7.4
Group, no. (%), y			Group, No. (%), y		
–4	19 (11)	17 (10)	–4	49 (29)	40 (24)
5 to 6	54 (32)	53 (31)	5 to 9	61 (36)	74 (44)
7 to 9	98 (57)	100 (59)	10 to 14	50 (29)	45 (26)
			15	11 (6)	11 (6)
Sex, no. (%)			Sex, no. (%)		
Girls	81 (47)	90 (53)	Girls	85 (50)	83 (49)
Influenza virus negative at baseline, no. (%)					
Yes	153 (90)	155 (91)			
Time from onset of influenza in index case to completion of study treatment			Rapid diagnostic test, no. (%)		
Mean ± SD, h	24.43 ± 11.26	22.75 ± 10.73	Positive	168 (98)	168 (99)
Group, No. (%)			Laboratory-confirmed influenza infection, no. (%)		
<24 hrs	88 (51)	89 (52)	Virus type and subtype, No. (%)		
			A/H1N1pdm09	1 (1)	0 (0)
Vaccinated for 2014/2015 season, no.(%)			A/H1N1	0 (0)	0(0)
Yes	71 (42)	69 (41)	A/H3N2	165 (97)	168 (99)
Relationship to the index case, no. (%)			B	2 (1)	0 (0)
Sibling	161 (94)	161 (95)	Mixed	0 (0)	0 (0)
Child	10 (6)	9 (5)	Negative	3 (2)	2 (1)

2009H1N1, influenza A(H1N1)pdm09; A/H3N2, influenza A(H3N2); B, influenza B.

[a] More than 1 subject could be enrolled for each index case. In this case, the index case was counted once for each household member who was enrolled. Of the 304 index cases (FAS) enrolled, 269 were associated with 1 subject, 33 with 2 subjects, and 2 with 3 subjects. In this table, the number "N" of household members and index cases in each treatment group is identical.

TABLE 2 Protective Effects of Laninamivir Against Influenza Infection

Outcome	Laninamivir 20 mg, no./total (%)	Placebo, no./total (%)	*P*[a]	RRR[b] (95% CI)
Primary end point				
Clinical influenza (FAS)	18/171 (11)	33/170 (19)	.02	45.8 (7.5 to 68.2)
Secondary end points				
Symptomatic influenza (FAS)	26/171 (15)	45/170 (27)	.01	42.6 (11.4 to 62.8)
Asymptomatic influenza (FAS)	12/171 (7)	16/170 (9)	.44	25.4 (−52.8 to 63.6)
Influenza infection[c]	20/153 (13)	46/155 (30)	<.001	56.0 (29.2 to 72.6)

RRR, relative risk reduction.

[a] Analyzed by using Fisher's exact test.

[b] 100 × (1 − Laninamivir/Placebo)

[c] Denominators are subpopulation of subjects in the FAS who had tested negative for influenza virus at baseline for each group.

TABLE 3 Subgroup Analyses for Clinical Influenza (FAS)

Subgroup	Laninamivir 20 mg, no./total (%)	Placebo, no./total (%)	*P*[a]	RRR[b] (95% CI)
Age, y				
<7 y	6/73 (8)	16/70 (23)	.02	64.0 (13.4 to 85.1)
≥7 y	12/98 (12)	17/100 (17)	.42	28.0 (−42.8 to 63.7)
Sex				
Girls	9/81 (11)	18/90 (20)	.14	44.4 (-16.6 to 73.5)
Boys	9/90 (10)	15/80 (19)	.12	46.7 (−15.1 to 75.3)
Time from onset of influenza in index case to completion of study treatment				
<24 h	10/88 (11)	18/89 (20)	.15	43.8 (−14.8 to 72.5)
≥24 h	8/83 (10)	15/81 (19)	.12	48.0 (−16.0 to 76.7)
Vaccinated for 2014/2015 season				
No	14/100 (14)	22/101 (22)	.20	35.7 (−18.3 to 65.1)
Yes	4/71 (6)	11/69 (16)	.06	64.7 (−5.7 to 88.2)
Infection in previous seasonal influenza				
No	14/121 (12)	31/137 (23)	.02	48.9 (8.5 to 71.4)
Yes	4/50 (8)	2/33 (6)	1.0	−32.0 (−580.1 to 74.4)
Relationship to index case				
Sibling	18/161 (11)	33/161 (21)	.03	45.5 (7.2 to 67.9)
Child	0/10 (0)	0/9 (0)	—	—

RRR, relative risk reduction

[a] Analyzed by using Fisher's exact test.

[b] 100 × (1 − Laninamivir/Placebo).

in laninamivir octanoate and placebo groups, respectively).

Subgroup analyses (Table 3) revealed that in the population <7 years the proportion of subjects who developed clinical influenza was significantly reduced by a single 20-mg dose of laninamivir octanoate ($P = .02$), whereas in the population ≥7 years the proportion in the laninamivir octanoate group appeared to be lower without statistical significance. Among contacts whose index cases were infected with the influenza A(H3N2) virus, laninamivir octanoate was also effective. The study revealed equivocal significance between placebo and laninamivir octanoate groups in the vaccination subgroups ($P = .06$).

Safety and Tolerability

A single 20-mg dose of laninamivir octanoate was well tolerated. No subjects withdrew from the study after administration. In the safety analysis set (341 subjects), the incidence of adverse events was 15% (25/171) in the laninamivir octanoate group and 13% (22/170) in the placebo group (Table 4). All adverse events were considered mild or moderate, and few were considered to be related to the study drug (1% in both laninamivir and placebo groups). No deaths, serious adverse events, or abnormal behavior were reported. Although the subjects were limited (2% and 5% in the laninamivir and placebo groups, respectively), the incidence of adverse events among the subgroup of high risk subjects (such as those with chronic respiratory diseases) was similar to the overall result (data not shown). No abnormal hematology and blood chemistry

TABLE 4 Incidence of Adverse Events

	Laninamivir 20 mg ($N = 171$), no. (%)	Placebo ($N = 170$), no. (%)
Adverse events	25 (15)	22 (13)
Drug-related adverse event	2 (1)	1 (1)
Serious adverse events	0	0
Adverse event leading to discontinuation of study drug	0	0
Abnormal behavior	0	0
Adverse events by MedDRA[a] preferred term, reported by ≥ 2 subjects		
Bronchitis	1 (1)	2 (1)
Gastroenteritis	1 (1)	3 (2)
Nasopharyngitis	7 (4)	2 (1)
Pharyngitis	2 (1)	2 (1)
Upper respiratory tract inflammation	5 (3)	6 (4)
Blood urine present	0	2 (1)
Protein urine present	0	2 (1)

MedDRA, Medical Dictionary for Regulatory Activities.
[a] MedDRA/J Version: 17.1.

values were observed in ≥2 subjects in the laninamivir octanoate group (Table 4). No abnormal behavior was observed.

DISCUSSION

Household members are at great risk of secondary infection when an index member is infected by the influenza virus. The risk of complications of influenza-associated encephalitis/encephalopathy and abnormal behavior are high, particularly in young Japanese children. Therefore, influenza prophylaxis in pediatric patients is of particular importance.

In this study, a single 20-mg dose of laninamivir octanoate significantly lowered the risk of developing clinical influenza, the primary end point, in children ≤10 years of age, compared with placebo in the FAS of the primary population.

Since a single 20-mg dose of laninamivir octanoate revealed prophylactic effect, the regimen in the current study is a highly user-friendly option. Although the numbers of infected individuals may differ by season, the number needed to treat based on the incidence of clinical influenza for the 2 groups in the current study was 11.

The FAS included subjects who had tested virus positive at registration, and subjects with household index cases who had tested virus negative at registration. In the analysis of population excluding such subjects, the relative risk reduction revealed greater reduction (64.5%), compared with the results for the FAS. This finding indicates that laninamivir octanoate prevents transmission of influenza to noninfected individuals within the household as an effective prophylaxis. Laninamivir potently inhibits the neuraminidase activities of various influenza A and B viruses. Neuraminidase activity is vital for viral release from host cells and viral spread. Because viral multiplication had already initiated in the host cells for subjects infected with influenza virus,[24] the regimen of the current study may be insufficient for preventing the development of influenza illness in patients who have been already infected with influenza before prophylaxis.

Regarding age category (<7 years), the proportion of subjects who developed clinical influenza was significantly reduced in the laninamivir octanoate group ($P = .02$). For age category ≥7 years, the significance level was not achieved. This age group was inclusive of 9 out of 12 subjects who were household members of index cases who had tested influenza virus-negative and subjects who had tested virus-positive at baseline. As stated above, there is a tendency of reduced efficacy in such subjects. In the evaluation of population excluding such cases, the incidence was 4% (3/84) in the laninamivir octanoate group and 14% (12/88) in placebo ($P = .03$; data not shown). In the subgroup of subjects who were infected with the previous seasonal influenza virus, the efficacy of the regimen was similar to that of placebo. A possible explanation for this result could be the preventive effect against the development of influenza caused by acquired immunity via infection with the previous seasonal influenza affecting the results regardless of prophylactic treatment. However, because the proportions of clinical influenza cases were as low as 4/50 (8%) and 2/33 (6%) in the respective groups, possibility of the protective effect of this regimen in this subgroup cannot be denied (Table 3). Statistical significance was not reached for both groups treated and untreated with 2014/2015 season vaccination. Therefore, the effect of vaccination on the efficacy of laninamivir octanoate is inconclusive in the current study. Studies have revealed that vaccines containing formerly prevalent strains are expected to be less effective against virus variants revealing antigenic drift. Prediction of future variations is not possible because the mechanism related to antigenicity still remains a mystery.[25] Given such circumstances, antiinfluenza prophylaxis could be useful as an adjunct to influenza vaccine.

Single 20-mg dose of laninamivir octanoate was well tolerated without the incidence of associated

safety concerns. Survey was performed prospectively between the 2007/2008 and 2012/2013 seasons, and retrospectively for the 2006/2007 season regarding abnormal behavior associated with influenza. As the result of the investigation, 858 cases were reported and among of them 95.7% were positive by the influenza rapid diagnosis test.[4] As in these findings, children with influenza virus infection often show abnormal behavior during the febrile period regardless of antiinfluenza drug exposure.[3–5] In this study, the association of laninamivir octanoate with abnormal behavior was investigated because it was also administered to subjects who had not developed influenza. No abnormal behavior was observed in all 153 subjects who had not developed influenza in the current study. Hence, the proposed regimen does not appear to induce abnormal behavior.

A limitation of this study is that we were unable to evaluate efficacy by subgrouping the subjects on the basis of virus types of the index-infected cases. This was because the vast majority of the index cases were infected with influenza A(H3N2; 98%). In a nonclinical study, laninamivir octanoate has been shown to exhibit neuraminidase inhibitory activity against both influenza A(H1N1)pdm09 and influenza B viruses.[10,11] In addition, the influenza A(H1N1)pdm09 virus cross-resistant to oseltamivir and peramivir detected during the 2013/2014 season in Japan remained sensitive to laninamivir.[9] Therefore, this regimen may be effective for preventing the development of influenza against these virus types, and further evaluation is necessary.

Although the diagnostic kits used were unspecified, the specificity of the rapid diagnostic test performed on the index cases was 98.5% (336/341). The value was comparable with the value described in the previous meta-analytic study (98.2%).[26] The specificity might have been high because all index cases in this study were tested within 48 hours from onset, when influenza activity was high[27] and also because rapid diagnostic test is a ubiquitous technique used for prescribing NAIs in Japan.

Another limitation is that very few subjects considered being at high risk, such as patients with chronic respiratory disease, were enrolled in the study. Generally, antiviral chemoprophylaxis is considered for persons at high risk of developing complications from influenza, including persons with chronic respiratory illness, metabolic disorders including diabetes mellitus, chronic heart disease, or immunodeficiency.[28] Further studies regarding the prophylactic administration of laninamivir octanoate in such subjects are necessary.

CONCLUSIONS

Single 20-mg dose of inhaled laninamivir octanoate was sufficient to protect against influenza in pediatric (≥2 years and <10 years of age) household members of index cases for prophylaxis of influenza, and laninamivir octanoate can be recommended as an option for prevention of influenza. Additionally, this regimen was well tolerated. This suggests that laninamivir octanoate should be a safe and useful agent as chemoprophylaxis. These results may provide some evidence that this regimen could be effective for preventing the development of influenza in pediatric household members of index cases for 10 days.

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ABBREVIATIONS

CI: confidence interval
FAS: full analysis set
NAI: neuraminidase inhibitor

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