MAJOR ARTICLE

Long-Acting Neuraminidase Inhibitor Laninamivir Octanoate versus Oseltamivir for Treatment of Influenza: A Double-Blind, Randomized, Noninferiority Clinical Trial

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Background. A single administration of laninamivir octanoate, a long-acting neuraminidase inhibitor, against influenza infection has been proven effective in nonclinical studies. This study evaluated the clinical efficacy of laninamivir octanoate for the treatment of adult influenza patients.

Methods. A double-blind, randomized controlled trial examined whether laninamivir octanoate was noninferior to oseltamivir. A total of 1003 patients aged ⩾20 years with febrile influenza symptoms for no more than 36 h were randomized to receive either 40 mg of laninamivir octanoate, 20 mg of laninamivir octanoate, or oseltamivir. Laninamivir octanoate was inhaled once on day 1, and oseltamivir (75 mg) was administered orally twice daily for 5 days. The primary end point was the time to illness alleviation.

Results. A total of 996 patients were included in the primary analysis (40-mg laninamivir octanoate, $n = 334$; 20-mg laninamivir octanoate, $n = 326$; and oseltamivir, $n = 336$). The median time to illness alleviation in the 40-mg laninamivir octanoate, 20-mg laninamivir octanoate, and oseltamivir groups was 73.0, 85.8, and 73.6 h, respectively. The difference between laninamivir octanoate and oseltamivir was −0.6 h (95% confidence interval, −9.9 to 6.9 h) for the 40-mg group and 12.2 h (95% confidence interval, −1.5 to 17.2 h) for the 20-mg group. The upper limits of the 95% confidence intervals were less than the prespecified noninferiority margin (18 h). The proportion of patients shedding virus at day 3 was significantly lower in the 40-mg laninamivir octanoate group than in the oseltamivir group ($P = .006$).

Conclusions. A single inhalation of laninamivir octanoate is effective for the treatment of seasonal influenza, including that caused by oseltamivir-resistant virus, in adults.

Clinical trials registration. NCT00803595.

Influenza epidemics have raised medical and social concerns because they are associated with considerable morbidity and mortality [1]. Neuraminidase inhibitors have been preferred for the treatment of influenza infections [2]. However, the isolation of influenza virus strains that are resistant to neuraminidase inhibitors has been reported, and the spread of drug-resistance has become a major concern [3–8]. In addition, the World Health Organization declared that infections caused by the novel swine-origin H1N1 influenza viruses had reached the pandemic phase in June 2009 [9], and oseltamivir-resistant 2009 pandemic H1N1 viruses have been detected in several countries [10].

Laninamivir octanoate (CS-8958; Daiichi Sankyo) is an octanoyl ester prodrug of laninamivir that exhibits neuraminidase inhibitory activity against influenza A and B viruses, including oseltamivir-resistant viruses [11] and 2009 pandemic H1N1 viruses [12]. Moreover,

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laninamivir octanoate has long-lasting antiviral activities. Nonclinical studies in mice showed that the efficacy of a single administration of laninamivir octanoate was similar to that of multiple administrations of zanamivir or oseltamivir [13] and that laninamivir was retained in the respiratory tract for a long time [14]. Laninamivir was slowly eliminated from healthy volunteers, lasting for up to 6 days after a single inhalation [15].

Considering these potential advantages, laninamivir octanoate promises to be a convenient anti-influenza agent if it is indeed efficacious as a standard anti-influenza treatment. We conducted a randomized controlled trial to determine whether the efficacy of a single inhalation of laninamivir octanoate was noninferior to that of oseltamivir administered with multiple oral doses in treating adults with seasonal influenza.

METHODS

Study design and patients. This multicenter, double-blind, randomized controlled trial was conducted from November 2008 through March 2009 at 117 institutions in Japan, Taiwan, Korea, and Hong Kong. The study was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board of each institution. Written informed consent was obtained from each patient.

Eligible patients were aged ⩾20 years who presented within 36 h after the onset of influenza symptoms and who had an axillary temperature of ⩾37.5°C and a positive test result with use of a rapid influenza diagnostic kit. The exclusion criteria were as follows: suspicion of infection with a bacterial species or noninfluenza virus within 1 week before enrollment; reported occurrence of any influenza-like symptom within 1 week before the onset of influenza; chronic respiratory disease; renal dysfunction; history of alcohol or drug abuse; or treatment with amantadine, zanamivir, or oseltamivir within 4 weeks. Pregnant women, breast-feeding women, and women who wished to become pregnant during the period of the trial were also excluded.

Randomization and masking. Patients were randomly assigned (1:1:1) to a 40-mg laninamivir octanoate, a 20-mg laninamivir octanoate, or an oseltamivir treatment group. Laninamivir octanoate was delivered by oral inhalation with use of the dry powder inhaler. Laninamivir octanoate was administered as a single inhalation on day 1. Oseltamivir (75 mg) was administered orally twice daily for 5 days (days 1–5). The computer-generated block random allocation sequence was provided by Acronet Corporation and was stratified according to the institution and type of influenza virus on the basis of the results of a rapid diagnostic kit capable of separately detecting influenza A and B. The patients, investigators, and trial personnel were blinded to the allocation sequence throughout the trial with use of a double-dummy method. The administration of laninamivir octanoate and the first dose of oseltamivir were confirmed by an investigator. Patients were allowed to use acetaminophen as a rescue medication for symptom relief, and its use was recorded. The concomitant use of other drugs was prohibited for 15 days.

Procedures. Medical histories, vital signs, physical examinations, and baseline virological samples were obtained before treatment. Hematology, blood chemistry, and urinalysis were performed on days 1 (baseline) and 15 for safety assessment. Patients recorded their axillary temperature and severity of influenza symptoms (headache, myalgia/arthralgia, fatigue, chills/sweats, nasal symptom, sore throat, and cough) 4 times daily for 15 days. The severity of each influenza symptom was graded into 4 categories (0, absent; 1, mild; 2, moderate; 3, severe) and was measured as the symptom score.

Influenza was screened using a rapid diagnostic kit (mainly Capilia FluA+B [Tauns] and QuickVue Rapid-SP influ [Quidel]) [16, 17], and results were confirmed using laboratory virological tests. Anterior nose and/or posterior pharyngeal throat swabs were taken on days 1 (baseline), 3, and 6 ($\pm$1 day for days 3 and 6) and were placed in viral transport medium. The swab samples were eluted and frozen at -80°C $\pm$ 10°C until use. For the baseline assessment, the subtype of influenza was determined based on an amplified DNA size by a reverse transcription polymerase chain reaction (RT-PCR) with subtype-specific primers designed from the hemagglutinin sequences of the seasonal H1N1, H3N2, and B viruses. Susceptibilities to laninamivir and oseltamivir carboxylate were determined by a fluorescence-based neuraminidase inhibition assay [12] with use of culture supernatants propagated once from the thawed swab samples in Madin-Darby canine kidney cells. The detection of the oseltamivir-resistant H274Y mutation (N2 numbering) was performed using an RT-PCR–restriction fragment length polymorphism assay according to the reported procedure [18]. Virus titers were determined using the swab samples obtained at 3 time points. The thawed swab samples were serially diluted and cultured for 7 days in Madin-Darby canine kidney cells. Based on the dilution factor showing no cytopathic effect, the virus titers were calculated as the $\log_{10}$ 50% tissue culture infective dose per mL of the viral transport medium, according to the Behrens-Kärber equation [19]. Serum samples were obtained on days 1 and 22 and were used to perform a hemagglutination-inhibition assay. The serological response was defined as a 4-fold or greater increase in subtype-specific antibody on day 22, compared with that on day 1. When the subtype of influenza could not be determined using RT-PCR, it was determined using the hemagglutination-inhibition assay. If the sample results were negative by both RT-PCR and hemagglutination-inhibition assay, the patient was regarded as not having a laboratory-confirmed influenza virus infection. All the virological tests were performed at Mitsubishi Chemical Medience.

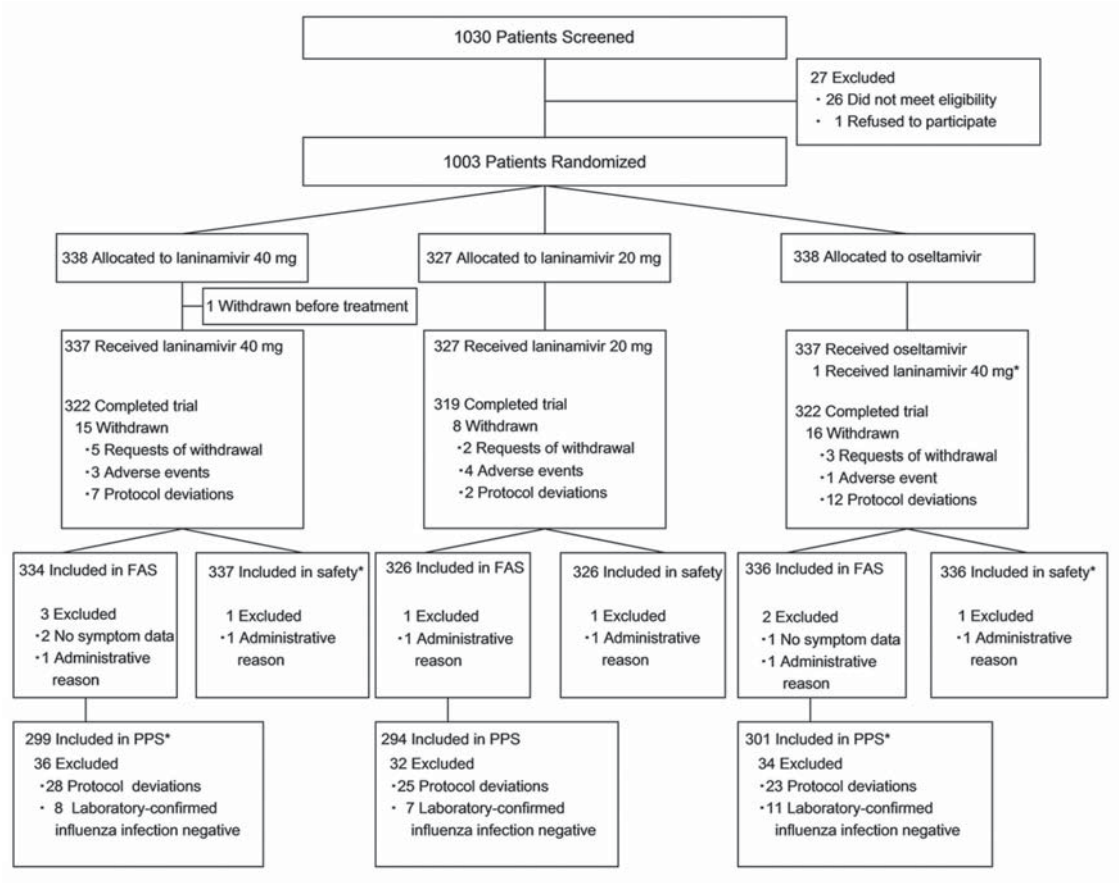

Figure 1. Patient flow chart. *One patient who was allocated to the oseltamivir group received 40 mg of laninamivir octanoate. This patient was included in the originally allocated group in the full analysis set (FAS) but was analyzed according to the actually administered treatment in the per protocol set (PPS) and safety analysis set.

Study outcomes. The primary end point was the time to illness alleviation, defined as the time from the initiation of trial treatment to the beginning of the first 21.5-h period in which all influenza symptoms were "absent" or "mild." The time to illness alleviation was defined as reported in a trial for oseltamivir [20–23]. Patients whose influenza symptoms had not been alleviated at the time of their withdrawal from the study or at the end of the observation period were censored. The time to the return of a normal body temperature was defined as the time until the beginning of the first 21.5-h period in which the axillary temperature returned to ≤36.9°C. The proportion of patients shedding viruses at each time point was calculated for each group.

Statistical analysis. This trial was designed to confirm the efficacy of laninamivir octanoate by showing that the median time to illness alleviation in patients treated with laninamivir octanoate was not >18 h longer than that in patients treated with oseltamivir. A noninferiority margin of 18 h was set to assure the superiority of laninamivir octanoate over a putative placebo. A meta-analysis using 3 placebo-controlled trials reported that the difference between the median time to illness alleviation in the placebo and oseltamivir groups was 33.1 h and the 95% confidence interval (CI) ranged from 19.1 to 47.1 h [20]. From this, a margin that was less than the lower limit of this 95% CI was selected. Based on the results of a phase II trial of laninamivir octanoate conducted in Japan (A.W. and Y.O., unpublished data), a sample size of 300 patients in each group was determined to achieve a power of at least 80% to show noninferiority at both dose levels of laninamivir octanoate with use of a Monte Carlo simulation.

To test the trial hypothesis, we calculated the differences in the median time to illness alleviation between each dose level of laninamivir octanoate and the oseltamivir group and the 2-sided nonparametric 95% CIs on the basis of the generalized Wilcoxon test. We then determined whether the upper limit of each 95% CI was <18 h in the 40-mg group and the 20-mg group, sequentially. As ancillary analyses, generalized Wilcoxon tests were performed between each comparison of the treatment groups. These analyses were also performed in subgroups stratified according to the type of influenza virus. All analyses were

Table 1. Baseline Characteristics of 996 Patients Included in the Full Analysis Set

Characteristic	Laninamivir 40 mg (n = 334)	Laninamivir 20 mg (n = 326)	Oseltamivir (n = 336)
Age			
Mean years ± SD	34.9 ± 11.5	35.6 ± 11.7	34.7 ± 11.3
Range, years	20–73	20–73	20–77
Male sex	179 (53.6)	162 (49.7)	178 (53.0)
Received vaccination against influenza	50 (15.0)	67 (20.6)	64 (19.0)
Laboratory-confirmed influenza infection[a]			
A/H1N1	218 (65.3)	215 (66.0)	212 (63.1)
A/H3N2	108 (32.3)	102 (31.3)	112 (33.3)
B	0 (0.0)	2 (0.6)	1 (0.3)
Negative	8 (2.4)	7 (2.1)	11 (3.3)
Axillary temperature at enrollment, mean °C ± SD	38.54 ± 0.72	38.56 ± 0.72	38.47 ± 0.78
Symptom score at enrollment,[b] mean score ± SD	11.4 ± 3.2	11.3 ± 3.1	11.4 ± 3.7
Duration of illness before treatment, mean h ± SD	23.52 ± 8.27	24.01 ± 7.89	24.25 ± 8.28
Outpatient	334 (100)	325 (99.7)	332 (98.8)
Concomitant disease	125 (37.4)	117 (35.9)	120 (35.7)

NOTE. Data are no. (%) of patients, unless otherwise indicated. SD, standard deviation.

[a] All patients included in the full analysis set had a positive result of the rapid diagnostic test.

[b] Symptom scores are described in the Methods section.

performed using SAS System, version 8.2 (SAS Institute). All reported P values were 2-sided without adjustments for multiple testing.

In the efficacy analysis, the full analysis set [24] based on the intention-to-treat principle was defined as the primary analysis set, and the per protocol set [24] was used in the sensitivity analysis. These analysis sets were used because the full analysis set and per protocol set are equally important in a noninferiority trial [25]. The safety analysis included all the patients who had received at least 1 dose of trial treatment and had at least 1 safety assessment.

RESULTS

A total of 1003 patients were enrolled (Figure 1). Of these, 4 patients were excluded from all the analyses; 1 patient discontinued the trial before receiving any treatment, and the informed consent of 3 patients was inappropriate (the partners of 2 patients signed the informed consent document, and 1 patient signed another person's name). Three other patients did not record their influenza symptoms and were excluded from the full analysis set. A total of 996 patients were included in the full analysis set (40-mg laninamivir octanoate, n = 334; 20-mg laninamivir octanoate, n = 326; and oseltamivir, n = 336). Of these, 1 patient did not receive the treatment as allocated; this patient was included in the originally allocated treatment group in the full analysis set but was analyzed according to the actually administered treatment in the per protocol set and safety analysis set.

The baseline characteristics were well balanced among the 3 groups in the full analysis set (Table 1) and in the per protocol set (data not shown). All the patients in the full analysis set had positive results with the rapid diagnostic kits. Laboratory virological tests were negative for influenza infection in 26 patients, and these patients were excluded from the per protocol set. Most patients were infected with influenza A (645 patients with H1N1 and 322 patients with H3N2), and only 3 patients were infected with influenza B. All the H1N1 strains carried the H274Y mutation except for viruses from 2 patients. The median 50% inhibitory concentration (IC_{50}) of oseltamivir carboxylate against the neuraminidase activity of the H1N1 strain was 690 nmol/L (range, 89–1500 nmol/L), whereas that of laninamivir was 1.70 nmol/L (range, 0.45–4.40 nmol/L). The median IC_{50} values of oseltamivir carboxylate and laninamivir against the H3N2 strain were 0.68 nmol/L (range, 0.27–1.40 nmol/L) and 2.30 nmol/L (range, 0.78–4.40 nmol/L), respectively.

The time courses for illness alleviation were similar among the 3 groups (Figure 2). In the full analysis set, the median time to illness alleviation was 73.0, 85.8, and 73.6 h in the 40-mg laninamivir octanoate, 20-mg laninamivir octanoate, and oseltamivir groups, respectively (Table 2). The differences between the respective dose levels for the laninamivir octanoate and oseltamivir groups were −0.6 h (95% CI, −9.9 to 6.9 h; P = .748) and 12.2 h (95% CI, −1.5 to 17.2 h; P = .104) for the 40-mg and 20-mg laninamivir octanoate groups, respectively. The upper limits of both 95% CIs were less than the prespecified noninferiority margin (18 h). However, the time to illness alleviation was significantly shorter in the 40-mg group than in the 20-mg laninamivir octanoate group (95% CI, −18.2 to −0.4 h; P = .038). The treatment effect in the 40-mg group was consistent in subgroup analyses according to

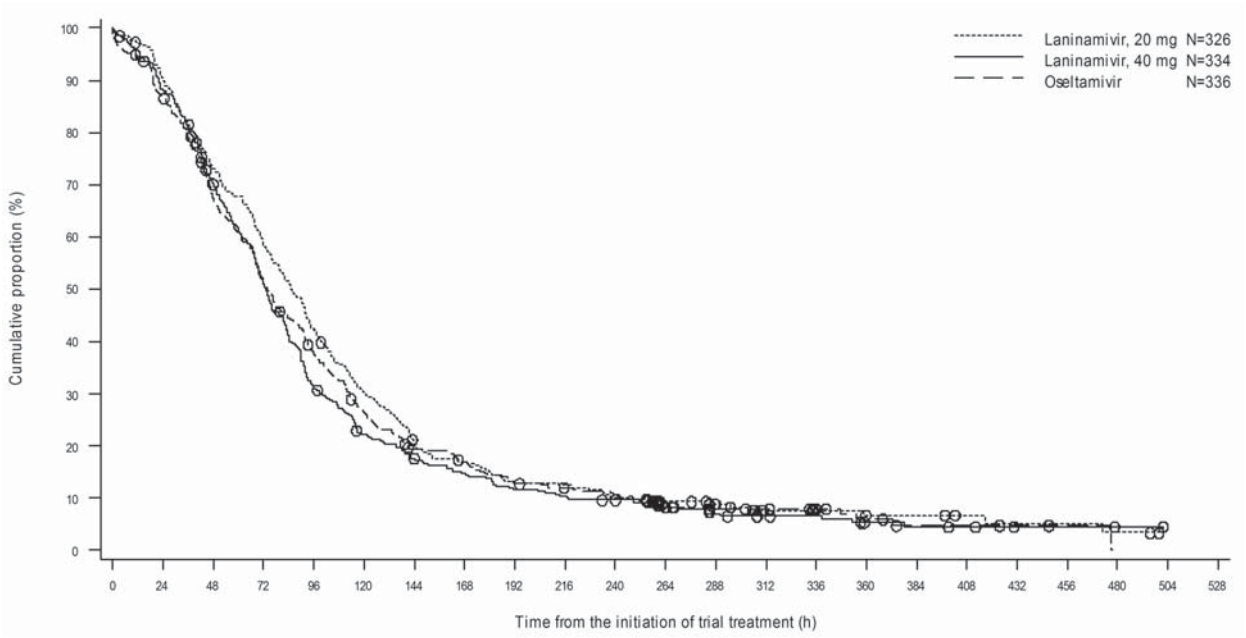

Figure 2. Time to illness alleviation in patients included in the full analysis set. The *open circles* indicate the patients whose influenza symptoms had not yet been alleviated by the time of their withdrawal from the study or the end of the observation period.

the virus subtype (H1N1 and H3N2). The median time for the return to a normal axillary temperature was 55.3, 58.0, and 54.7 h in the 40-mg laninamivir octanoate, 20-mg laninamivir octanoate, and oseltamivir groups, respectively. Similar results were also obtained from the per protocol set (Table 2).

The median virus titers and the proportions of patients shedding virus at baseline were similar among the 3 groups (Table 3). However, the proportion of patients shedding virus on day 3 was significantly lower in the 40-mg laninamivir octanoate group (27.6%) than in the oseltamivir group (37.7%), with an absolute difference of −10.1% (95% CI, −17.2% to −3.1%; $P = .006$). In the H1N1-infected subpopulation, the proportion of patients shedding virus on day 3 also differed significantly between these 2 groups, with an absolute difference of −14.7% (95% CI, −23.7% to −5.7%; $P = .001$).

Both drugs were well tolerated. The most common adverse events were gastrointestinal events such as diarrhea, nausea, and vomiting. The event rates for diarrhea were 7.7% (26 of 337 patients), 5.5% (18 of 326 patients), and 7.7% (26 of 336 patients) in the 40-mg laninamivir octanoate, 20-mg laninamivir octanoate, and oseltamivir groups, respectively. For nausea, the rates were 1.2% (4 of 337 patients), 2.1% (7 of 326 patients), and 1.8% (6 of 336 patients), respectively. For vomiting, the rates were 0.3% (1 of 337 patients), 0.3% (1 of 326 patients), and 2.4% (8 of 336 patients), respectively. These events were mild to moderate and resolved within several days. Mild to moderate dizziness was observed only in patients receiving laninamivir octanoate (3 [0.9%] of 337 patients in the 40-mg laninamivir octanoate group and 6 [1.8%] of 326 patients in the 20-mg laninamivir octanoate group), but none of the patients discontinued the trial because of dizziness.

DISCUSSION

The efficacy of a single inhaled dose of laninamivir octanoate was not inferior to that of 10 doses of oseltamivir administered orally over 5 days. A laninamivir octanoate dose of 40 mg was optimal, and the time to illness alleviation was shorter than that for a 20-mg dose.

During the 2008–2009 influenza season, oseltamivir-resistant H1N1 virus carrying the H274Y mutation spread worldwide [8]. Unexpectedly, ~65% of the patients in this study were infected with the oseltamivir-resistant H1N1 virus carrying the H274Y mutation. However, the median time to illness alleviation in the oseltamivir group (73.6 h) was similar to the times reported in other trials (70.0 to 87.4 h for oseltamivir groups vs 93.3–116.5 h for placebo groups) [20–23]. The important design features and the performance of the oseltamivir group in our trial were similar to those of other reports. Therefore, we concluded that our trial had a sufficient assay sensitivity [26] and was capable of confirming the efficacy of laninamivir octanoate.

Among the patients infected with H3N2 virus, the 40-mg laninamivir octanoate group showed similar efficacy to the oseltamivir group in both the duration of illness and virus shedding. These results were consistent with the IC_{50} values of oseltamivir

Table 2. Effects of Laninamivir Octanoate and Oseltamivir on Clinical Outcomes

Variable	Full analysis set			Per protocol set		
	Laninamivir 40 mg	Laninamivir 20 mg	Oseltamivir	Laninamivir 40 mg	Laninamivir 20 mg	Oseltamivir
Time to alleviation of influenza illness						
No. of patients	334	326	336	299	294	301
Median h (95% CI)[a]	73.0 (68.4–80.8)	85.8 (76.5–92.8)	73.6 (68.5–83.3)	74.0 (69.3–81.9)	82.5 (74.4–91.8)	71.3 (67.2–79.7)
Difference,[b] median h (95% CI)	−0.6 (−9.9 to 6.9)	12.2 (−1.5 to 17.2)	…	2.7 (−7.3 to 10.3)	11.2 (−1.2 to 17.8)	…
P[c]	.748	.104	…	.739	.089	…
Difference,[d] median h (95% CI)	−12.8 (−18.2 to -0.4)	…	…	−8.5 (−15.9 to 2.3)	…	…
P[c]	.038	…	…	.146	…	…
Time to alleviation of influenza illness (A/H1N1)						
No. of patients	218	215	212	NA	NA	NA
Median h (95% CI)[a]	74.0 (69.3–82.0)	82.9 (73.0–91.8)	77.5 (70.2–93.8)	NA	NA	NA
Difference,[b] median h (95% CI)	−3.5 (−15.2 to 6.8)	5.4 (−10.7 to 11.6)	…	NA	NA	…
P[c]	.461	.914	…	NA	NA	…
Time to alleviation of influenza illness (A/H3N2)						
No. of patients	108	102	112	NA	NA	NA
Median h (95% CI)[a]	72.5 (57.8–88.6)	91.2 (71.6–116.8)	67.5 (53.5–76.3)	NA	NA	NA
Difference,[b] median h (95% CI)	5.0 (−7.3 to 19.8)	23.7 (3.4–38.7)	…	NA	NA	-
P[c]	.366	.014	…	NA	NA	-
Time for return to normal axillary temperature						
No. of patients	334	326	336	299	294	301
Median h (95% CI)[a]	55.3 (46.6–64.0)	58.0 (52.3–66.9)	54.7 (48.2–62.2)	55.3 (46.5–64.1)	57.2 (51.9–64.2)	52.3 (47.4–59.2)
Difference,[b] median h (95% CI)	0.6 (−5.8 to 5.7)	3.3 (−2.8 to 9.1)	…	3.0 (−4.7 to 7.2)	4.9 (−2.1 to 10.2)	…
P[c]	.981	.318	…	.699	.204	…

NOTE. CI, confidence interval; NA, not analyzed.

[a] Estimated by the Kaplan-Meier method.
[b] Compared with oseltamivir group.
[c] Analyzed using the generalized Wilcoxon test.
[d] Compared with laninamivir 20-mg group.

Table 3. Effects of Laninamivir Octanoate and Oseltamivir on Virus Titers

	Full analysis set, virus type								
	All types			A/H1N1			A/H3N2		
Variable	Laninamivir 40 mg	Laninamivir 20 mg	Oseltamivir	Laninamivir 40 mg	Laninamivir 20 mg	Oseltamivir	Laninamivir 40 mg	Laninamivir 20 mg	Oseltamivir
Day 1 (baseline)									
No. of patients	334	325	336	218	214	212	108	102	112
Virus titer, median log $TCID_{50}$/mL (range)	2.50 (1.5–7.5)	2.70 (1.5–7.5)	2.70 (1.5–7.5)	2.50 (1.5–7.5)	2.70 (1.5–7.5)	2.70 (1.5–7.5)	2.70 (1.5–5.5)	2.70 (1.5–6.0)	2.70 (1.5–5.7)
Shedding virus									
No. (%) of patients[a]	294 (88.0)	290 (89.2)	306 (91.1)	199 (91.3)	194 (90.7)	197 (92.9)	94 (87.0)	92 (90.2)	104 (92.9)
Difference,[b] % (95% CI)	−3.0 (−7.7 to 1.6)	−1.8 (−6.4 to 2.7)	…	−1.6 (−6.7 to 3.5)	−2.3 (−7.5 to 2.9)	…	−5.8 (−13.7 to 2.1)	−2.7 (−10.1 to 4.8)	…
P[c]	.208	.436	…	.593	.481	…	.180	.623	…
Day 3 (day 2–4)									
No. of patients	330	323	334	216	213	212	107	101	110
Virus titer, median log $TCID_{50}$/mL (range)	1.50 (1.5–5.0)	1.50 (1.5–6.0)	1.50 (1.5–7.5)	1.50 (1.5–5.0)	1.50 (1.5–4.5)	1.50 (1.5–4.7)	1.50 (1.5–3.7)	1.50 (1.5–3.5)	1.50 (1.5–4.3)
Shedding virus									
No. (%) of patients[a]	91 (27.6)	110 (34.1)	126 (37.7)	61(28.2)	68 (31.9)	91(42.9)	30 (28.0)	39 (38.6)	31 (28.2)
Difference,[b] % (95% CI)	−10.1 (−17.2 to -3.1)	−3.7 (−11.0 to 3.7)	…	−14.7 (−23.7 to -5.7)	−11.0 (−20.1 to -1.9)	…	−0.1 (−12.1 to 11.8)	10.4 (−2.3 to 23.1)	…
P[c]	.006	.330	…	.001	.021	…	>.99	.143	…
Day 6 (day 5–7)									
No. of patients	325	323	328	212	214	206	106	100	110
Virus titer, median log $TCID_{50}$/mL (range)	1.50 (1.5–2.0)	1.50 (1.5–1.7)	1.50 (1.5–2.2)	1.50 (1.5–2.0)	1.50 (1.5–1.7)	1.50 (1.5–2.2)	1.50 (1.5–1.5)	1.50 (1.5–1.5)	1.50 (1.5–1.5)
Shedding virus									
No. (%) of patients[a]	7 (2.2)	2 (0.6)	5 (1.5)	6 (2.8)	1 (0.5)	4 (1.9)	1 (0.9)	1 (1.0)	1 (0.9)
Difference,[b] % (95% CI)	0.6 (−1.4 to 2.7)	−0.9 (−2.5 to 0.7)	…	0.9 (−2.0 to 3.8)	−1.5 (−3.6 to 0.6)	…	0.0 (−2.5 to 2.6)	0.1 (−2.5 to 2.7)	…
P[c]	.576	.450	…	.751	.207	…	>.99	>.99	…

NOTE. CI, confidence interval; $TCID_{50}$, log_{10} 50% tissue culture infective dose.

[a] No. of patients with detectable virus (at least 1.5 log $TCID_{50}$/mL).

[b] Compared with oseltamivir group.

[c] Compared with oseltamivir group, by Fisher's exact test.

carboxylate and laninamivir against H3N2 virus. Among the patients infected with H1N1 virus carrying the H274Y mutation, the duration of illness had no significant difference between the 40-mg laninamivir octanoate group and the oseltamivir group. However, the durations of virus shedding in the 40-mg and 20-mg laninamivir octanoate groups were significantly shorter than in the oseltamivir group, in keeping with the IC_{50} values. Therefore, laninamivir might effectively inhibit the replication of oseltamivir-resistant H1N1 viruses.

In the parallel trial of pediatric patients, laninamivir octanoate reduced the duration of influenza illness significantly, compared with oseltamivir, against H1N1 virus with the H274Y mutation [27]. In addition, recent studies have found that the clinical efficacy of oseltamivir against H1N1 virus with the H274Y mutation was reduced, especially among children [28, 29]. Given these findings, the clinical efficacy of oseltamivir could be different in adults and in children against oseltamivir-resistant H1N1 virus. Considering that the course of influenza among children was more protracted with longer periods of virus shedding than in adults [3], it is possible that the difference between adult and children is related to the patients' immune status. In our study, most of the patients were aged 20–39 years and did not have any underlying diseases. In this population, it could be difficult to evaluate the difference of the clinical efficacy between laninamivir octanoate and oseltamivir against H1N1 virus with H274Y mutation. Further study will need to prove whether laninamivir octanoate has a positive impact on the clinical course of patients with oseltamivir-resistant virus infections.

Laninamivir octanoate was well tolerated. The most common adverse events were gastrointestinal events, but their rates were similar to those in the oseltamivir group. Although dizziness was observed only in the laninamivir octanoate groups, this symptom has been reported in 2% of patients treated with other neuraminidase inhibitors [30, 31].

Our trial excluded high-risk populations, such as patients with chronic respiratory disease. In addition, we did not have the chance to enroll patients infected with the 2009 pandemic H1N1 virus, which became widespread after the completion of our trial. The efficacy and safety of laninamivir octanoate in these populations should be evaluated in future trials. Nonclinical study results have shown that laninamivir octanoate is effective against the 2009 pandemic H1N1 virus [12]; thus, an assessment of its clinical efficacy is warranted.

In conclusion, a single inhalation of laninamivir octanoate was sufficient to treat adults with seasonal influenza including that caused by oseltamivir-resistant viruses. Furthermore, this treatment was well tolerated.

MULTINATIONAL ASIAN CLINICAL RESEARCH FOR INFLUENZA VIRUS EXTERMINATION ON LONG-ACTING NEURAMIDASE INHIBITOR (MARVEL) STUDY GROUP

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References

1. Nicholson KG, Webster RG, Hay AJ. Textbook of influenza. Oxford: Blackwell Science, **1998**.
2. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med **2005**; 353:1363–1373.
3. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir phosphate: descriptive study. Lancet **2004**; 364:759–765.
4. Le QM, Kiso M, Someya K, et al. Avian flu: isolation of drug-resistant H5N1 virus. Nature **2005**; 437:1108 [Erratum, Nature **2005**; 438:754].
5. Hatakeyama S, Sugaya N, Ito M, et al. Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. JAMA **2007**; 297: 1435–1442.
6. Meijer A, Lackenby A, Hungnes O, et al. Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007–08 season. Emerg Infect Dis **2009**; 15: 552–560.
7. Moscona A. Global transmission of oseltamivir-resistant influenza. N Engl J Med **2009**; 360:953–956.
8. World Health Organization. Influenza A virus resistance to oseltamivir and other antiviral medicines. June **2009**. http://www.who.int/csr/disease/influenza/2008-9nhemisummaryreport/en/print.html. Accessed 22 February 2010.
9. World Health Organization. World now at the start of 2009 influenza pandemic. June **2009**. http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html. Accessed 22 February 2010.
10. World Health Organization. Pandemic (H1N1) 2009—update 66. http://www.who.int/csr/don/2009_09_18/en/print.html. Accessed 22 February 2010.
11. Yamashita M, Tomozawa T, Kakuta M, Tokumitsu A, Nasu H, Kubo S. CS-8958, a prodrug of the new neuraminidase inhibitor R-125489, shows long-acting anti-influenza virus activity. Antimicrob Agents Chemother **2009**; 53:186–192.
12. Itoh Y, Shinya K, Kiso M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature **2009**; 460:1021–1025.
13. Kubo S, Tomozawa T, Kakuta M, Tokumitsu A, Yamashita M. Laninamivir prodrug CS-8958, a long-acting neuraminidase inhibitor, shows superior anti-influenza virus activity after a single administration. Antimicrob Agents Chemother **2010**; 54:1256–1264.
14. Koyama K, Takahashi M, Oitate M, et al. CS-8958, a prodrug of the novel neuraminidase inhibitor R-125489, demonstrates a favorable long-retention profile in the mouse respiratory tract. Antimicrob Agents Chemother **2009**; 53:4845–4851.
15. Ishizuka H, Yoshiba S, Okabe H, Yoshihara K. Clinical pharmacokinetics of laninamivir, a novel long-acting neuraminidase inhibitor, after single and multiple inhaled doses of its prodrug, CS-8958, in healthy male volunteers. J Clin Pharmacol [Epub ahead of print].
16. Kubo N, Ikematsu H, Nabeshima S, et al. Evaluation of an immunochromatography test kit for rapid diagnosis of influenza [in Japanese]. Kansenshogaku Zasshi **2003**; 77:1007–1014.
17. Yamazaki M, Mitamura K, Kimura K, et al. Clinical evaluation of an immunochromatography test for rapid diagnosis of influenza [in Japanese]. Kansenshogaku Zasshi **2001**; 75:1047–1053.
18. Guo L, Garten RJ, Foust AS, et al. Rapid identification of oseltamivir-resistant influenza A (H1N1) viruses with H274Y mutation by RT-PCR/restriction fragment length polymorphism assay. Antiviral Res **2009**; 82: 29–33.
19. Behrens B, Kärber G. Wie sind Reihenversuche für biologishe Auswertungen am zweckmäßigsten anzuordnen [in German]? Naunyn Schmiedebergs Arch Exp Pathol Pharmakol **1934**; 18:379–388.
20. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner DA, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. BMJ **2003**; 326:1235–1240.
21. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. JAMA **2000**; 283:1016–1024.
22. Nicholson KG, Aoki FY, Osterhaus ADME, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Lancet **2000**; 355:1845–1850 [Erratum, Lancet **2000**; 356:1856].
23. Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute influenza: placebo controlled double-blind multicenter phase III trial [in Japanese]. Kansenshogaku Zasshi **2000**; 74:1044–1061.
24. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline: Statistical principles for clinical trials. February **1998**. http://www.ich.org/cache/compo/276-254-1.html. Accessed 22 February 2010.
25. European Medicines Agency Committee for Medicinal Products for Human Use. Points to consider on switching between superiority and non-inferiority. July **2000**. http://www.emea.europa.eu/pdfs/human/ewp/048299en.pdf. Accessed 22 February 2010.
26. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline: choice of control group and related issues in clinical trials. July **2000**. http://www.ich.org/cache/compo/276-254-1.html. Accessed 22 February 2010.
27. Norio S, Yasuo O. Long-acting neuraminidase inhibitor laninamivir octanoate (CS-8958) versus oseltamivir as treatment for children with influenza virus infection. Antimicrob Agents Chemother **2010**; 54:2575–2582.
28. Kawai N, Ikematsu H, Iwaki N, et al. Clinical effectiveness of oseltamivir for influenza A(H1N1) virus with H274Y neuraminidase mutation. J Infect **2009**; 59:207–212.
29. Kawai N, Ikematsu H, Hirotsu N, et al. Clinical effectiveness of oseltamivir and zanamivir for treatment of influenza A virus subtype H1N1 with the H274Y mutation: a Japanese, multicenter study of the 2007–2008 and 2008–2009 influenza season. Clin Infect Dis **2009**; 49: 1828–1835.
30. GlaxoSmithKline. Relenza (zanamivir) inhalation powder highlights of prescribing information. February **2008**. http://us.gsk.com/products/assets/us_relenza.pdf. Accessed 22 February 2010.
31. Roche Laboratories Inc. Tamiflu (oseltamivir phosphate) capsules package insert. August **2008**. http://www.rocheusa.com/products/tamiflu/pi.pdf. Accessed 22 February 2010.