

A Double-Blind, Placebo-Controlled Study of Intravenous Peramivir in Acute Influenza Patients

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ABSTRACT

Background

Peramivir (PVR) is a novel neuraminidase inhibitor. In this Phase II study, efficacy, safety and pharmacokinetic (PK) profiles of a single-dose intravenous infusion of PVR were evaluated in patients with seasonal influenza.

Methods

This study was a randomized, double-blind, placebo-controlled trial conducted in Japan. Three hundred patients aged 20 to 64 years with a positive influenza rapid antigen test (RAT) were recruited within 48 hours of onset of influenza symptoms and randomized to one of the three treatment groups: PVR, 300 mg or 600 mg, or placebo (1:1:1), administered once I.V. on study day 1. Influenza symptoms and body temperature were self-assessed daily for 14 days. Nasal and pharyngeal swabs were taken to determine virus titer. The primary endpoint was time to alleviation of symptoms.

Results

Of the 300 patients, 296 were included in the intent-to-treat infected population (PVR 300 mg: 99, 600 mg: 97, placebo: 100). PVR significantly reduced time to alleviation of symptoms at 300 mg (hazard ratio, 0.681) and 600 mg (hazard ratio, 0.666) compared to placebo (adjusted p-value = 0.0046 for both comparisons). Change from baseline in Composite Symptom Score was significantly improved in both PVR 300 mg and 600 mg groups compared to the placebo group, as early as 24 hours after the start of treatment (p=0.0032 and 0.0109, respectively). There was a significant difference between PVR 600 mg and placebo in time-weighted change in influenza virus titer from baseline to two days after infusion (p=0.0027). No serious adverse events were reported. PVR was well tolerated, with a similar adverse event profile to that of placebo. PK profiles observed in influenza patients were similar to those seen in healthy subjects.

Conclusion

This study demonstrated that a single intravenous dose of PVR was effective and well tolerated in patients with seasonal acute influenza.

INTRODUCTION

Peramivir is a novel neuraminidase inhibitor with potent antiviral activity against various influenza A and B virus subtypes including avian influenza A(H5N1) both *in vitro* and *in vivo*. Peramivir showed strong affinity to influenza neuraminidase and slow off-rate (S. Bantia et al. *Antiviral Research* 2006). This suggests that peramivir can inhibit NA activity for a long period and that a single-dose IV infusion of peramivir would be effective for acute influenza infection.

Phase I studies of intravenous peramivir in healthy Japanese subjects demonstrated good tolerability, dose proportionality in C_{max} and AUC in plasma concentration (unpublished data).

According to these results, we expected that single-dose IV infusion of peramivir would be effective for acute influenza infection. So, we investigated the efficacy, safety and pharmacokinetics of single-dose, IV infusion of peramivir in Japanese acute influenza patients.

MATERIALS AND METHODS

This study was a multi-center, randomized, double-blind, placebo-controlled trial conducted in Japan.

<Objectives>

To evaluate the efficacy, dose response and safety of peramivir administered intravenously in single doses in patients with influenza virus infection.

[Primary objective]

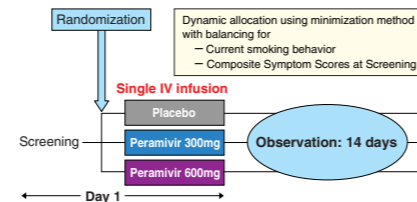
To evaluate the efficacy of peramivir administered at single intravenous doses of 300 mg and 600 mg, compared to placebo, using the time to alleviation of symptoms* as an endpoint. The primary efficacy analysis population was the intent-to-treat infected population (ITT).

*: Time to alleviation of symptoms is defined as the time from the start of study drug treatment to the time of recovery from influenza symptoms which is when all of the seven influenza symptoms become "0: none" or "1: mild" with the state lasting for at least 21.5 hours.

<Inclusion criteria>

- Provide a written informed consent to participate in this study
- Age: ≥20 years and <65 years
- Has a fever of ≥38.0°C
- Has at least two symptoms of moderate or greater severity due to influenza
- Within 48 hours from onset
- Positive rapid antigen test (RAT) for influenza

<Dosing methods>



<Evaluation of efficacy>

	Screening (Pre-dose)	Day 1						
		Visit 1 (Post-dose)	Visit 2 (Day 2)	Visit 3 (Day 3)	Visit 4 (Day 4)	Visit 5 (Day 9)	Visit 6 (Day 14)	
Patient's Demography	X							
Rapid antigen test (RAT kit)	X							
Study drug medication	X							
Patient diary	Body temperature	X	← Twice daily →					
	ISS	X	← Twice daily →					
	IWS	X	← Once daily →					
Nasal, throat swabs (virological tests)	X	If possible	X	X	X			
Plasma drug concentration		X	If possible	X				

ISS[®]: Influenza Symptom Severity Scale
7 influenza symptoms (cough, sore throat, headache, nasal congestion, feeling feverish or having chills, aches and pains of the muscle or joints, and fatigue) on a 4-grade (0-3 point) scale: (0=absent; 1=mild; 2=moderate, 3=severe).

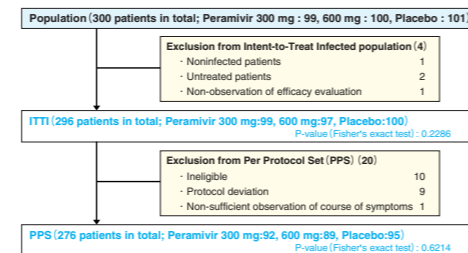
IWS[®]: Influenza Impact Wellbeing Scale

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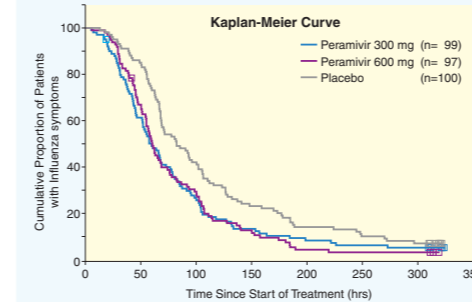
<PPK analysis methods>

Peramivir plasma concentration data in acute influenza patients along with those in healthy adult subjects were preliminarily analyzed by nonlinear mixed effect modeling using the NONMEM program to evaluate the population pharmacokinetic (PPK) parameters.

Efficacy analysis population (All randomized patients)



Time to alleviation of symptoms (ITT)



	Peramivir 300mg	Peramivir 600mg	Placebo
Patients Number	N=99	N=97	N=100
Median (hrs)	59.1	59.9	81.8
(95% Confidence Interval)	(50.9, 72.4)	(54.4, 68.1)	(68.0, 101.5)
Hazard ratio	0.681	0.666	—
Adjusted p-value (one-sided)	0.0046*	0.0046*	—

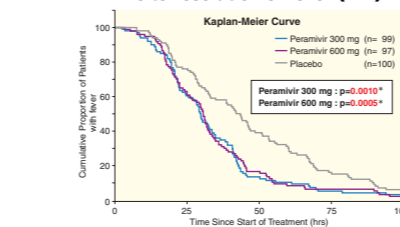
Analysis method: Cox proportional hazards model with adjusting for the current smoking behavior and composite seven symptom scores at baseline
Adjusted p-value: Determined by Hochberg method
*: statistical significance; Adjusted p-value (one-sided) < 0.025

Change in composite symptom scores from baseline at 24hr (ITT)

	Peramivir 300mg	Peramivir 600mg	Placebo
Observed Number	92	93	94
Mean ± SD (points)	-3.4 ± 3.1	-3.3 ± 3.3	-2.3 ± 3.1
Difference from Placebo (95% CI)	-1.25 (-2.07, -0.42)	-1.07 (-1.89, -0.25)	—
P-value (two-side)	0.0032*	0.0109*	—

Analysis method: Analysis of covariance with adjusting for the current smoking behavior and composite seven symptom scores at baseline
*: statistical significance; p-value (two-sided) < 0.05

Time to resolution of fever (ITT)



Analysis method: Stratified Log Rank Test with adjusting for the current smoking behavior and composite seven symptom scores at baseline
*: statistical significance; p-value (two-sided) < 0.05

Time to resumption of normal activity (ITT)

	Peramivir 300mg	Peramivir 600mg	Placebo
Median (hrs)	125.6	129.7	173.8
(95% Confidence Interval)	(103.8, 148.5)	(122.4, 170.7)	(146.0, 200.9)
Improvement over Placebo (hrs)	-48.2	-44.8	—
P-value	0.0407*	0.0310*	—

Time to resumption of normal activity is defined as the time from the start of study drug treatment to the time point of where daily living activity is resumed. The time of resumption of daily activity is when the activity assessment (IWS) becomes 10.
Analysis method: Stratified log rank test
*: statistical significance; p-value (two-sided) < 0.05

RESULTS

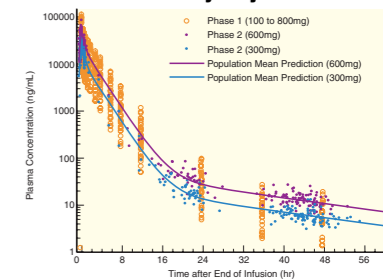
Summary of adverse events

	Adverse Events		
	Peramivir 300mg N=99	Peramivir 600mg N=97	Placebo N=100
Number of Events	252	252	257
Number of Patients (%)	87 (87.9)	90 (90.9)	91 (91.0)
95% Confidence Interval (%)	(79.8, 93.6)	(83.4, 95.8)	(83.6, 95.8)
P-value*	0.4986	1.0000	—
Main Adverse events*			
Clinical symptoms	36 (36.4)	41 (41.4)	45 (45.0)
Diarrhea	14 (14.1)	15 (15.2)	17 (17.0)
Nausea	3 (3.0)	6 (6.1)	1 (1.0)
Vomiting	0 (0.0)	3 (3.0)	2 (2.0)
Bronchitis	3 (3.0)	0 (0.0)	3 (3.0)
Nasopharyngitis	0 (0.0)	4 (4.0)	6 (6.0)
ECG QT prolonged	2 (2.0)	1 (1.0)	3 (3.0)
Dizziness	3 (3.0)	2 (2.0)	2 (2.0)
Abnormal Laboratory Changes	82 (82.8)	81 (81.8)	80 (80.0)
Monocyte percentage increased	20 (20.2)	18 (18.2)	31 (31.0)
Blood glucose increased	18 (18.2)	17 (17.2)	18 (18.0)
Lymphocyte percentage increased	14 (14.1)	14 (14.1)	5 (5.0)
β2 microglobulin urine increased	14 (14.1)	8 (8.1)	11 (11.0)
Protein urine present	9 (9.1)	11 (11.1)	18 (18.0)

*: P-value Comparison vs Placebo
+: For clinical symptoms, more than 3 events; For abnormal laboratory changes, more than 10 events

No Serious Adverse Events (SAE) were reported in this study.

PPK analysis with influenza patients and healthy subjects



	Population Mean		Individual Bayesian Estimation			
	Mean	CV (%)	Healthy Subject		Patient	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
CL (L/hr)	6.49	(11.5)	6.19	(9.72)	6.59	(11.8)
Vss (L)	16.8	*	17.2	(7.02)	16.9	(7.81)

*: CV (%) for V₁, V₂ and V₃ were 19.9, 10.3 and not estimated, respectively.

Since 15% of the injection volume remained in the cannula into the patients' venous, the doses for the patients in phase 2 were adjusted at the reduction of 15% to estimate the PPK parameters.

CONCLUSION

- A single intravenous dose of peramivir was effective in patients with seasonal acute influenza compared to placebo.
- No serious adverse events were reported. Peramivir was well tolerated, with a similar adverse event profile to that of placebo.
- PK profiles observed in influenza patients were similar to those seen in healthy subjects in our phase I studies.