

# Efficacy and Safety of Intravenous Peramivir in Children with 2009 Pandemic A (H1N1) Influenza Virus Infection

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## Abstract

### 1. Background

Peramivir is a new neuraminidase inhibitor for intravenous administration that was first introduced in clinical practice for adult patients in Japan. The US Food and Drug Administration had issued an emergency use authorization for peramivir exclusively for severe pandemic A (H1N1) influenza virus infection. Peramivir exhibits high inhibitory activity (IC<sub>50</sub>) against pandemic A (H1N1) influenza virus\*, raising expectations that it would be clinically effective.

### 2. Materials and methods

A multicenter, open-label, uncontrolled study was conducted in children with influenza virus infection ranging in age from ≥28 days to <16 years during the 2009 pandemic A (H1N1) influenza epidemic to evaluate the efficacy, safety, and pharmacokinetics of peramivir after intravenous infusion of 10 mg/kg (600 mg maximum) once daily for up to 5 days. From Day 2 onward, peramivir was allowed to be administered when patients had a body temperature of ≥38.0°C or when additional administration was considered to be needed by the investigator based on clinical symptoms.

### 3. Results

Among the 115 children (125 days to 15 years old) confirmed to have influenza virus infection by rapid antigen test and treated with peramivir, and whom efficacy data were available, the median time to alleviation of symptoms was 27.9 hours (95% confidence interval: 21.7 - 31.7), and the median time to resolution of fever (<37.5°C) was 20.4 hours (95% confidence interval: 19.1 - 20.9). The proportion of virus-positive patients was 78.2% on Day 2 after the start of treatment, and it decreased to 7.1% on Day 6. Adverse events and adverse drug reactions were reported in 62.4% and 29.1%, respectively, of the patients. The most commonly observed adverse events were gastrointestinal disorders, including diarrhea and vomiting, abnormal leukocyte cell count, including decreased neutrophil count and increased eosinophil count, and abnormal behavior. All of these adverse events and adverse drug reactions resolved or improved rapidly. The plasma concentrations in the pediatric patients were much higher than the IC<sub>50</sub> of peramivir and within the range of the plasma concentrations in adults of which the efficacy and safety had been demonstrated.

### 4. Conclusions

Intravenous administration of peramivir for 1 or 2 days at 10mg/kg (maximum 600mg) was found to be clinically and virologically effective and safe in children with pandemic A (H1N1) influenza virus infection.

## About Peramivir

- Intravenous neuraminidase inhibitor
- Strong affinity to influenza neuraminidase and slow off-rate
- Approved in Japan for adult in Jan 2010
- Emergency use authorization (EUA) for pandemic A (H1N1) influenza in US

## Study Design and Methods

|                     |  |
|---------------------|--|
| Design              | • Multi-center, open-label, non-controlled study   |
| Subjects            | • Age: 28 days to <16 years old<br>• Influenza patients with positive rapid antigen test<br>• Onset of influenza ≤48 hours   |
| Treatment           | • Peramivir 10mg/kg (maximum 600mg) IV qd (up to 5 days)<br>• After Day 2, if the patient meets "additional administration criteria", same dosage of peramivir as Day 1 could be administered. [Additional-administration criteria] fever of ≥38.0°C or the investigator's decision based on the clinical symptoms |
| Primary endpoint    | • Time to alleviation of influenza symptoms  |
| Secondary endpoints | • Time to resolution of fever<br>• Virological efficacy<br>• Incidence of adverse events and adverse drug reactions<br>• Plasma concentration of peramivir   |
| Period              | • From Sep to Dec, 2009, Japan<br>• [During the pandemic influenza A (H1N1) epidemic]  |

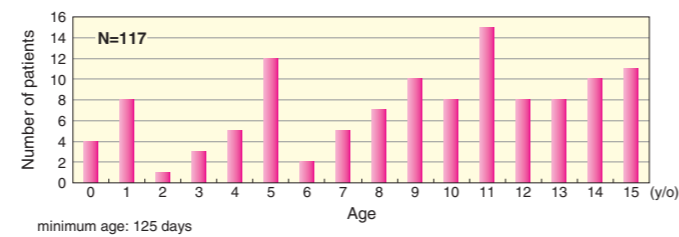
## Result

**Table 1. Demographic parameters**

| Backgrounds                         | category                      | total N=117 |
|-------------------------------------|-------------------------------|-------------|
| Gender                              | Male                          | 61 (52.1%)  |
|                                     | Female                        | 56 (47.9%)  |
| Time to onset* of influenza (hrs)   | 0-24                          | 91 (77.8%)  |
|                                     | 24-48                         | 26 (22.2%)  |
|                                     | >48                           | 0 (0.0%)    |
| Influenza rapid antigen test        | Type A                        | 117 (100%)  |
|                                     | Type B                        | 0           |
| Virus type/subtype confirmed by PCR | Pandemic A (H1N1) 2009        | 108 (92.3%) |
|                                     | Type A (subtype not detected) | 1 (0.9%)    |
|                                     | Virus type not detected       | 8 (6.8%)    |

The duration of treatment was 1 day in 107 patients (91.5%) and 2 days in 10 patients (8.5%). None of the patients was treated for 3 days or more.

**Figure 1. Age distribution**



**Table 2. Neuraminidase inhibitory activity (IC<sub>50</sub>) against the virus isolated at the time of enrollment**

| Total N=115 | peramivir (nM) | oseltamivir (nM) | zanamivir (nM) |
|-------------|----------------|------------------|----------------|
| Min.        | 0.281          | 0.418            | 0.820          |
| Median      | 0.3510         | 0.5170           | 1.0420         |
| Max.        | 0.483          | 1.362            | 1.526          |

**Table 3. Time to alleviation\* of symptoms**

|             | Total        | 28 days to <2 years | 2 to <6 years | 6 to <12 years | 12 to <16 years |
|-------------|--------------|---------------------|---------------|----------------|-----------------|
| N           | 115**        | 12                  | 20            | 46             | 37              |
| Median (hr) | 27.9         | 31.0                | 26.4          | 25.6           | 29.1            |
| (95% CI)    | (21.7, 31.7) | (20.8, 50.9)        | (17.8, 68.9)  | (20.8, 31.7)   | (20.9, 36.3)    |

\*"Alleviation" is defined as "none" or "mild" for both "cough" and "runny nose/nasal stuffiness", and body temperature (axillary) of <37.5°C for at least 21.5 hrs.  
 \*\* 2 subjects were excluded since they have no data after treatment.

**Table 4. Time to resolution\* of fever**

|             | Total        | 28 days to <2 years | 2 to <6 years | 6 to <12 years | 12 to <16 years |
|-------------|--------------|---------------------|---------------|----------------|-----------------|
| N           | 115**        | 12                  | 20            | 46             | 37              |
| Median (hr) | 20.4         | 20.8                | 20.7          | 19.7           | 20.4            |
| (95% CI)    | (19.1, 20.9) | (19.8, 31.5)        | (17.0, 25.0)  | (17.1, 21.1)   | (18.6, 21.9)    |

\*"Resolution" is defined as <37.5°C for at least 21.5 hrs.  
 \*\* 2 subjects were excluded since they have no data after treatment.

**Table 5. Proportion of virus-positive patients\***

|      | Total          | 28 days to <2 years | 2 to <6 years | 6 to <12 years | 12 to <16 years |
|------|----------------|---------------------|---------------|----------------|-----------------|
| Day1 | 100% (101/101) | 100% (9/9)          | 100% (17/17)  | 100% (42/42)   | 100% (33/33)    |
| Day2 | 78.2% (79/101) | 66.7% (6/9)         | 76.5% (13/17) | 81.0% (34/42)  | 78.8% (26/33)   |
| Day6 | 7.1% (7/99)    | 22.2% (2/9)         | 17.6% (3/17)  | 5.0% (2/40)    | 0.0% (0/33)     |

\*A subset of patients who were positive for influenza virus titer assay at baseline

## [Efficacy Evaluation]

- Peramivir exhibited a strong neuraminidase inhibitory activity (IC<sub>50</sub> of 0.281-0.483 nM) against the pandemic A (H1N1) influenza viruses. [Table 2]
- The median time to alleviation of symptoms and time to resolution of fever were 27.9 hours and 20.4 hours, respectively. [Table 3, 4]
- In a previous study in adults, the median time to alleviation of symptoms ranged from 59.1 to 59.9 hours, although the study in adults was conducted during 2007-2008 season. [Kohno S *et al.*, 48<sup>th</sup> Annual ICAAC/IDSA 46<sup>th</sup> Annual Meeting (2008)]
- Iris W Li *et al.* reported a time to resolution of fever (≤37.2°C) of 1.4 days in 118 adults and children aged 2 years or older with pandemic A (H1N1) influenza after treatment with oseltamivir [CHEST 2010].
- The results of the present study showed that pediatric patients recuperated rapidly, suggesting high therapeutic efficacy of peramivir against pandemic A (H1N1) influenza.

**Table 6. Adverse events and adverse drug reactions**

|                                 | Total N=117  | 28 days to <2 years N=12 | 2 to <6 years N=21 | 6 to <12 years N=47 | 12 to <16 years N=37 |
|---------------------------------|--------------|--------------------------|--------------------|---------------------|----------------------|
| <b>[Adverse Events]</b>         |              |                          |                    |                     |                      |
| N (cases)                       | 73 (116)     | 9 (17)                   | 14 (20)            | 30 (52)             | 20 (27)              |
| incidence (%)                   | 62.4%        | 75.0%                    | 66.7%              | 63.8%               | 54.1%                |
| (95%CI)                         | (53.0, 71.2) | (42.8, 94.5)             | (43.0, 85.4)       | (48.5, 77.3)        | (36.9, 70.5)         |
| <b>[Adverse Drug Reactions]</b> |              |                          |                    |                     |                      |
| N (cases)                       | 34 (45)      | 5 (6)                    | 8 (9)              | 12 (17)             | 9 (13)               |
| incidence (%)                   | 29.1%        | 41.7%                    | 38.1%              | 25.5%               | 24.3%                |
| (95%CI)                         | (21.0, 38.2) | (15.2, 72.3)             | (18.1, 61.6)       | (13.9, 40.3)        | (11.8, 41.2)         |

The incidence of adverse events did not differ according to the duration treatment.

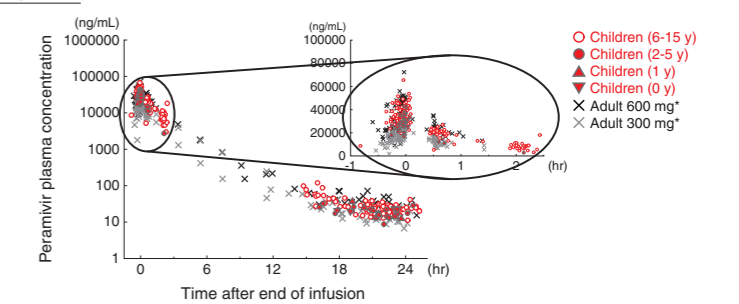
**Table 7. Major adverse events (incidence >2%)**

| Adverse events                            | Total N=117 | 28 days to <2 years N=12 | 2 to <6 years N=21 | 6 to <12 years N=47 | 12 to <16 years N=37 |
|---|-------------|--------------------------|--------------------|---------------------|----------------------|
| <b>[Clinical symptoms]</b>                |             |                          |                    |                     |                      |
| Diarrhoea                                 | 19 (16.2%)  | 3 (25.0%)                | 6 (28.6%)          | 4 (8.5%)            | 6 (16.2%)            |
| Vomiting                                  | 11 (9.4%)   | ---                      | 3 (14.3%)          | 7 (14.9%)           | 1 (2.7%)             |
| Abdominal pain                            | 3 (2.6%)    | ---                      | 1 (4.8%)           | 1 (2.1%)            | 1 (2.7%)             |
| Abnormal behaviour                        | 3 (2.6%)    | ---                      | 1 (4.8%)           | 1 (2.1%)            | 1 (2.7%)             |
| <b>[Abnormal laboratory test results]</b> |             |                          |                    |                     |                      |
| Neutrophil count decreased                | 25 (21.4%)  | 4 (33.3%)                | 2 (9.5%)           | 12 (25.5%)          | 7 (18.9%)            |
| Eosinophil count increased                | 9 (7.7%)    | ---                      | 1 (4.8%)           | 7 (14.9%)           | 1 (2.7%)             |
| White blood cell count decreased          | 4 (3.4%)    | ---                      | ---                | 2 (4.3%)            | 2 (5.4%)             |
| Urine ketone body present                 | 4 (3.4%)    | ---                      | 2 (9.5%)           | 2 (4.3%)            | ---                  |
| Protein total decreased                   | 3 (2.6%)    | 3 (25.0%)                | ---                | ---                 | ---                  |

## [Safety Evaluation]

- Most of the events were mild or moderate and resolved without intervention.
- The reported adverse events are often observed in patients with influenza, especially in children.
- There were no adverse events that caused termination of treatment with peramivir.
- Peramivir was well tolerated.

**Figure 2. Plasma concentrations**



\*Kohno S *et al.*, 48<sup>th</sup> Annual ICAAC/IDSA 46<sup>th</sup> Annual Meeting (2008)

The plasma concentrations in pediatric patients were within the range of plasma concentrations in adults which were confirmed to be clinically effective and safe.