

Clinical and Virologic Outcomes with Peramivir Therapy in Hospitalized Adults with Influenza B: Sub-Group Analysis of a Phase 2 Trial

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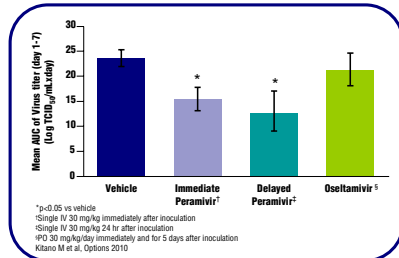
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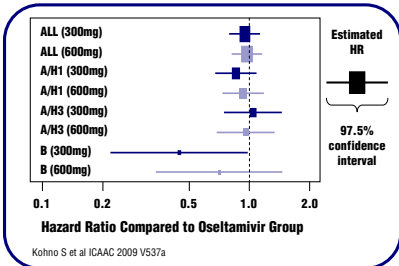
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INTRODUCTION

- Peramivir is an intravenous neuraminidase inhibitor approved for the treatment of influenza in Japan and South Korea and in Phase 3 trials in the rest of the world.
- Peramivir is more potent against influenza B than oseltamivir
 - In vitro, the IC₅₀ of peramivir ranged from 0.6 to 11 nM compared with an IC₅₀ for oseltamivir carboxylate of 6.4 to 24.3 nM¹
 - Influenza B isolates from untreated subjects during the 1999-2000 influenza season in Canada showed a mean IC₅₀ of 0.87 nM for peramivir compared with 11.53 nM for oseltamivir carboxylate²
 - IV peramivir prophylaxis or treatment improved viral titers and symptoms of cynomolgus macaques with influenza B, superior to the effects of oseltamivir treatment³



- In Phase 1 trials, peramivir-treated subjects showed linear, dose-dependent increases in plasma concentrations with mean C_{max} ranging from 1925 ng/mL (0.5 mg/kg) to 44667 ng/mL (8 mg/kg)^{4,5}, far above those levels required for influenza B viral inhibition
- In a completed Phase 3 trial in over 1000 outpatients with influenza in Asia, subjects infected with influenza B demonstrated a significant reduction in viral titers when treated with a single dose of IV peramivir 300 mg (n=21) compared with oseltamivir (n=23)⁶



- In a completed Phase 2 trial (BCX1812-201), clinical and laboratory assessments demonstrated similar clinical courses and outcomes in a population of hospitalized subjects with influenza A or B treated with peramivir or oseltamivir⁷, but clinical response data by type of infecting virus were not separately examined at that time
- Because the susceptibility of influenza B virus to peramivir is greater than to oseltamivir and higher levels of drug are achieved in subjects infected with influenza B, peramivir treatment may result in better therapeutic efficacy than oseltamivir
- We conducted a post-hoc sub-group analysis of the 32 hospitalized subjects infected with influenza B in trial BCX1812-201 to determine the virologic outcomes and possible clinical correlates after receiving IV peramivir or PO oseltamivir

METHODS

Study Subjects

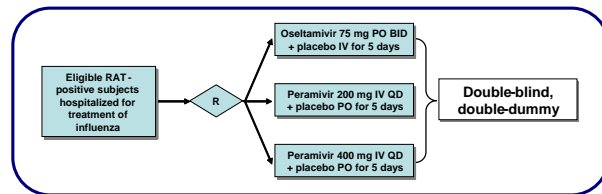
- ≥ 18 years old
- Onset of acute illness ≤ 72 hr before presentation
- Fever or history of fever within 24 hr
- ≥ 1 respiratory (e.g., cough) and 1 constitutional (e.g., fever) symptom
- Positive RAT test for influenza B

Study Subjects, cont.

- Hospitalized with at least one of the following conditions
 - ≥ 60 years old
 - COPD or other chronic lung disease requiring daily medication
 - NYHA class I or II congestive heart failure or angina
 - Diabetes mellitus
 - Transcutaneous oxygen saturation < 94%
 - Systolic blood pressure < 90 mmHg
 - Severe illness in the opinion of the investigator
- No severe comorbid conditions
- No recent antiviral treatment (≤ 7 days) or live virus immunization (≤ 21 days)
- No evidence of current non-influenza infectious illness

Study Design and Treatment

- Randomized, double-blind, double-dummy study conducted at 84 sites in 7 countries from July 2007 to Sept 2008
- Eligible subjects were hospitalized and randomly assigned to 1 of 3 treatment groups



- Subjects discharged from the hospital prior to Day 5 received remaining doses as outpatients
- Concomitant use of zanamivir, oseltamivir, amantadine, and/or rimantadine was prohibited except for clinical relapse
- Parenteral corticosteroids and immunizations were prohibited during the study
- Follow-up visits were conducted on Day 10 and Day 14 (or early termination)

Study Assessments

- Efficacy
 - Time to clinical stability based on normalization of vital signs and O₂ saturation collected twice daily on days 1-5, 10, and 14
 - Time to normal temperature collected twice daily on days 1-5, 10, and 14
 - Time to return to usual activities collected once daily on diary cards
- Virology
 - Influenza B infection determined by PCR
 - Nasopharyngeal specimens collected at enrollment, 12, 24, 36, 48, 72, and 96 hr post-enrollment and hospital discharge
 - Quantitative viral burden was evaluated by determination of log₁₀ tissue culture infective dose₅₀ (TCID₅₀)
 - Neuraminidase enzyme inhibition (NAI) assay was performed on virus MDCK culture supernatants from baseline clinical isolates by MUNANA technique to assess the IC₅₀ of peramivir, oseltamivir and zanamivir

RESULTS

Subjects

- Influenza B was confirmed by PCR in 32 of the 137 subjects enrolled in BCX1812-201
- Mean age of the influenza B population was 59.6 (range 19-95), with 56% males
- 72% of subjects had symptom onset < 48 hours before enrollment
- 11 subjects received oseltamivir and 21 subjects received peramivir
- For the sub-group analysis, data were combined for subjects receiving 200 mg and 400 mg peramivir

Efficacy

Efficacy Results in Subjects with Influenza B

	Peramivir (n=21)	Oseltamivir (n=11)	P value
Time to Clinical Stability median hr (95% CI)	31.0 (21.2, 48.4)*	41.8 (28.1, 68.0)*	0.38
Time to Normal Temperature median hr (95% CI)	24.3 (13.1, 47.7)	35.5 (12.1, 48.5)	0.78
Time to Return to Normal Activities median days (95% CI)	6.4 (3.5, NA)	10.0 (2.7, NA)	0.95

*Based on 17 peramivir- and 10 oseltamivir-treated subjects clinically unstable at baseline

Safety

Subjects with Adverse Events

	Peramivir (n=21)	Oseltamivir (n=11)
All Adverse Events	14 (67%)	4 (36%)
Grade 3 or 4 Adverse Events	3 (14%)	1 (9%)
Serious Adverse Events	2 (10%)	0
Deaths	0	0

- The most common adverse events in subjects treated with either peramivir or oseltamivir (reported ≥ 3 times) were nausea, diarrhea, and hypokalemia
- Grade 3 or 4 hyperglycemia, hypokalemia, and hypotension were reported in subjects receiving peramivir; cough was reported in a subject receiving oseltamivir
- Two subjects receiving peramivir developed pneumonia that prolonged hospitalization; one of these also experienced gastrointestinal hemorrhage, anemia, and urinary retention. None of these SAEs were judged related to drug treatment.

Virology

Baseline Viral Titers (log₁₀ TCID₅₀/mL) in Subjects with Influenza B

	Peramivir (n=21)	Oseltamivir (n=11)	P value
Mean (SD)	4.1 (1.0)	4.2 (1.8)	0.78*
Median	4.3	4.5	
Min, Max	2.5, 6.0	0.8, 7.3	

*Overall Treatment P value based on Wilcoxon Rank Sum Test

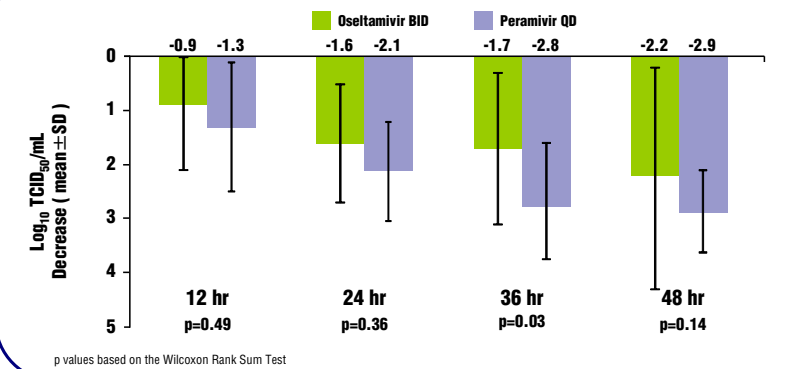
ACKNOWLEDGMENTS

The authors acknowledge the study participants, investigators, study site personnel, and BioCryst study team who participated in BCX1812-201 and HHS/BARDA for funding support. The authors acknowledge the assistance of Elizabeth Field in preparing the poster, which was funded by BioCryst. The authors also acknowledge Kitano M, Infectious Diseases, Medicinal Research Laboratories, Shionogi and Co. Ltd, Osaka, Japan, and Kohno S, Nagasaki University School of Medicine, Nagasaki, Japan.

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Viral Titer Change From Baseline For Subjects With Influenza B



Neuraminidase Enzyme Inhibition Results of Initial Influenza B Isolates, IC₅₀ nM

	Peramivir	Oseltamivir	Zanamivir
Mean (SD)	6.2 (5.8)	36.8 (25.6)	8.9 (8.7)
Median	4.3	28.5	4.8
Min, Max	0.3, 22.1	3.9, 102.6	1.1, 32.1

DISCUSSION

- Peramivir and oseltamivir treatment resulted in similar clinical outcomes in the overall study population (N=137) of the BCX1812-201 study⁷
- However, in the sub-group of influenza B infected patients (N=32) in BCX1812-201, peramivir treatment resulted in more rapid reduction of viral replication and showed a trend to more rapid normalization of clinical outcomes
- The reduction in viral titers following peramivir compared with oseltamivir confirmed previously seen results in animals³ and humans⁶
- The NAI assay results demonstrated that influenza B viruses were 6.5-fold more susceptible to peramivir than oseltamivir and confirm results from previous studies^{1,2}
- Resumption of normal activities 4 days earlier in peramivir-treated subjects may be a clinically meaningful outcome

CONCLUSIONS

- Peramivir appeared to be clinically better than oseltamivir in the treatment of adults hospitalized with influenza B.
- Peramivir resulted in more rapid reduction of viral titers than oseltamivir.
- These findings may reflect superior antiviral activity of peramivir against influenza B and should be further investigated.