

# A Placebo-Controlled Evaluation of the Safety and Pharmacokinetics of Multiple-Dose Intravenous Administration of Peramivir to Healthy Elderly Subjects

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## Introduction

Influenza virus causes an acute viral disease of the respiratory tract. It is an important disease for several reasons, including ease of communicability, short incubation time, rapid rate of viral mutation, morbidity associated with resultant loss of productivity, severity of complicating diseases and increased risk of death, particularly in the elderly. Hospitalizations due to influenza occur more frequently in the elderly and the risks of complications and/or mortality from influenza are highest in this age group. This study (BCX1812-104) was conducted to evaluate the safety and pharmacokinetics of peramivir, a potent neuraminidase inhibitor<sup>1</sup> suitable for parenteral administration, in an elderly population  $\geq 65$  years of age. Results from this study were also used to compare pharmacokinetic results from an adult population 18-49 years of age<sup>2</sup>.

## Methods and Materials

In this study twenty (20) healthy subjects  $\geq 65$  year received intravenous peramivir (4 mg/kg BID) on Day 1 and thereafter, two cohorts of 8 subjects each (6 peramivir; 2 placebo) received 4 mg/kg BID for either 5d or 10d, commencing on Day 3 of the study. Samples for PK analyses were obtained and safety monitoring included assessment of adverse events, clinical laboratory studies, and 24-hour urine collections.

Table 1. Demographics of Elderly Population.

	Day 1 1 Day BID	Cohort A 5 Days BID	Cohort B 10 Days BID
N	20	6	6
Mean Age	70.6	67.5	70.7
Range	65-79	65-71	66-75
Gender: Males	10 (50%)	2 (33%)	2 (33%)
Females	10 (50%)	4 (67%)	4 (67%)

## Results

Table 2. Peramivir Pharmacokinetic Parameters in an Elderly Population

PK Parameters Mean ( $\pm$ SD) %CV	Day 1 1 Day BID	Day 7** Cohort A 5 Days BID	Day 12** Cohort B 10 Days BID
N	20	6	6
C <sub>max</sub> (ng/mL)	23600 $\pm$ 4458 21.3%	22608 $\pm$ 4910 21.7%	22933 $\pm$ 2951 12.0%
AUC <sub>0-12</sub> (ng h/mL)	622953 $\pm$ 7452 14.3%	70465 $\pm$ 12236 17.4%	61572 $\pm$ 8564 13.9%
T <sub>1/2,z</sub> (h)	ND	14.6 $\pm$ 1.8 12.5%	16.3 $\pm$ 3.5 12.5%
CL (mL/h/kg)	ND	58.2 $\pm$ 10.2 17.6%	66.3 $\pm$ 11.5 17.4%

\*\* PK parameters computed from the last dose from the last sampling day 7 or 12.

Figure 1. Peramivir Concentration-Time Profile, Day 1 (4 mg/kg BID), Day 7 ( Cohort A), and Day 12 (Cohort B) .

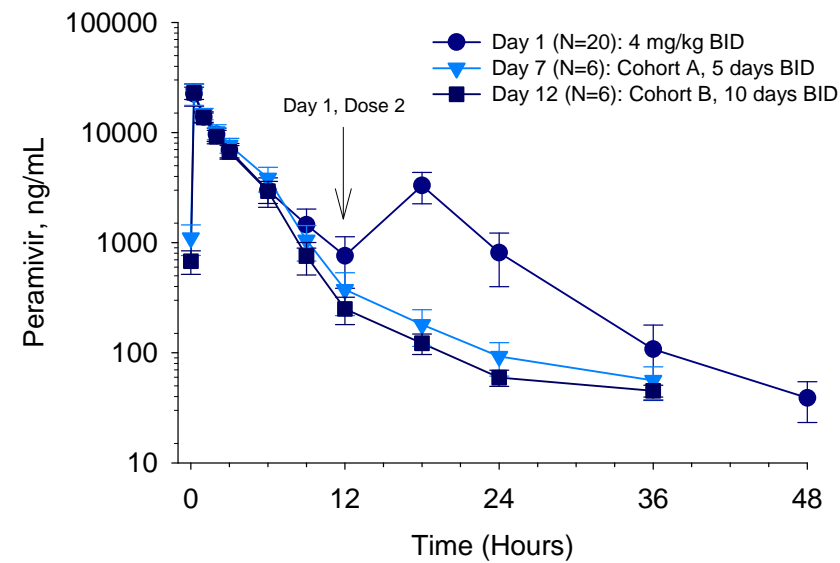


Figure 2. Daily Peramivir Concentration-Time Profile: Cohort A and Cohort B.

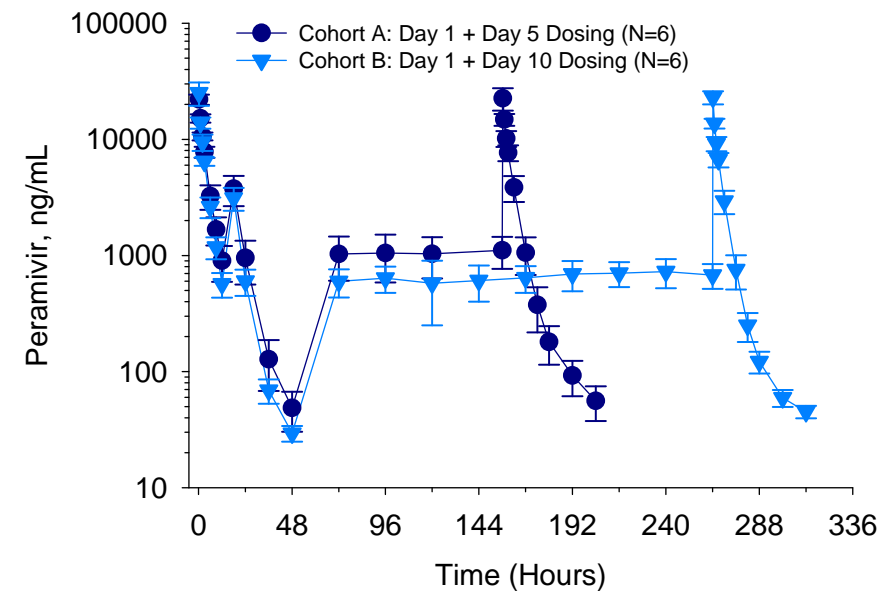
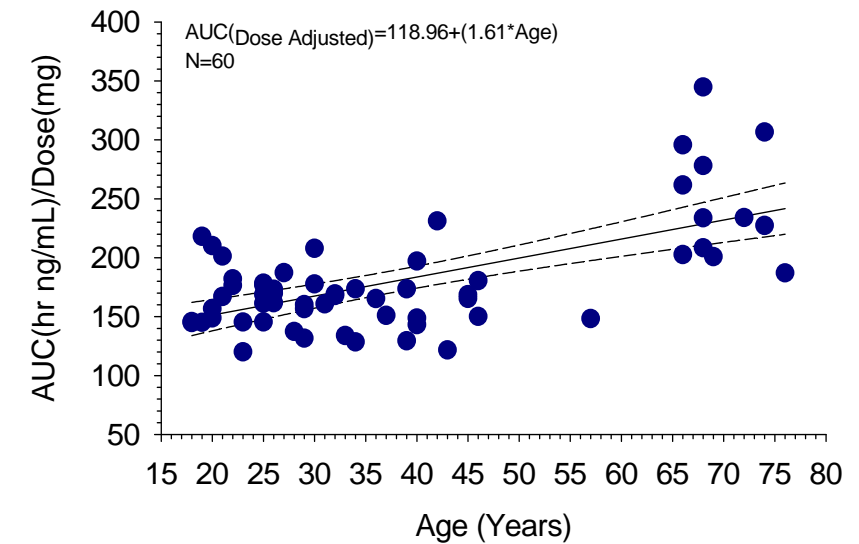


Figure 3. Comparison of Age and Dose Adjusted AUC<sub>0-12</sub> in adult and elderly subjects.



## Safety

Serial ECG monitoring resulted in no findings considered related to treatment. Changes in clinical chemistry, hematology and urinalysis results were unremarkable. No serious adverse events were reported.

## Conclusions

There was no evidence of drug accumulation over either 5 or 10 days. When data were compared with those of subjects aged 18-50 years from study BCX1812-103<sup>2</sup>, elderly subjects had a 46% increase in dose-normalized AUC. This increase is likely attributed to reduced renal function evident in elderly subjects. Similar increases in dose-adjusted AUC in elderly subjects have been reported for oseltamivir<sup>3</sup>. This study provides pharmacokinetic information in an elderly age group and suggests an acceptable safety profile with multiple-day, twice-daily intravenous administration of peramivir. Clinical studies to evaluate the efficacy and safety of peramivir in the treatment of influenza in the hospital setting are in progress.

## References

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