

Pharmacokinetic and Safety Evaluations of Escalating Doses of Peramivir Administered Intravenously in Healthy Volunteers

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Introduction

Peramivir is a potent neuraminidase inhibitor with potential efficacy in treatment of uncomplicated and severe human influenza infections.

Methods and Materials

In three Phase 1 studies (BCX1812-101, -102, -103), healthy subjects received peramivir (n=61) or placebo (n=23). In study 101 subjects received single doses of peramivir 0.5 mg/kg or placebo; study 102 peramivir 0.5 mg/kg BID or placebo; study 103 single peramivir doses of 1, 2, 4, and 8 mg/kg; 4 mg/kg BID on one day; and 2 mg/kg or 4 mg/kg BID for 10 days. Plasma and urine samples for pharmacokinetic analyses were collected as were serial laboratory assessments during and after treatment.

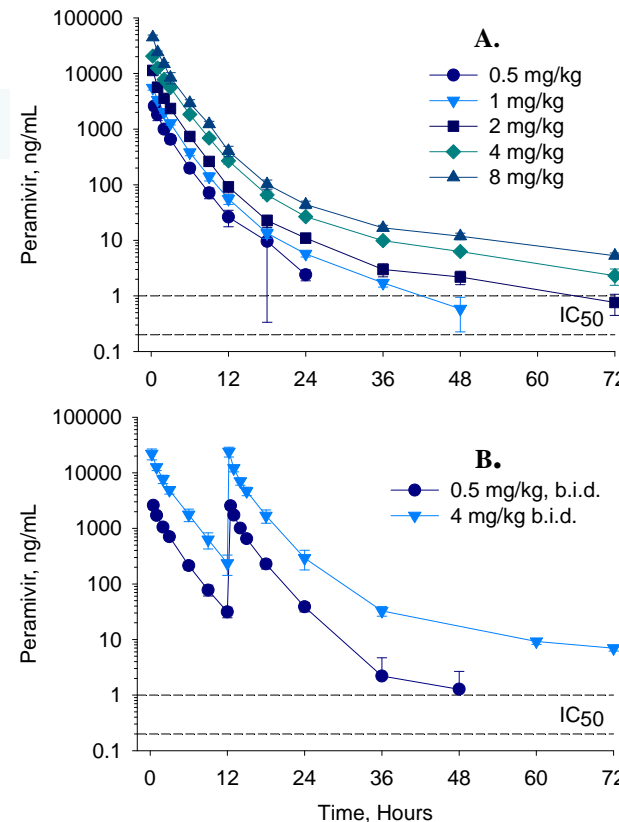
Results

Mean C_{max} ranged from 1925ng/mL (0.5 mg/kg) to 44667 ng/mL (8 mg/kg). The $AUC_{0-\infty}$ hr ranged from 4975 hr•ng/mL (0.5 mg/kg) to 90666 hr•ng/mL (8 mg/kg) following a single infusion. The mean $t_{1/2}$ for doses of 2 mg/kg to 8 mg/kg ranged from 15.9 hr to 20.8 hr. Peramivir clearance was similar across all dose groups and no significant accumulation occurred with dosing for 10 days. No serious adverse events occurred. The overall incidence of treatment-emergent adverse events was similar among subjects who received intravenous infusions of peramivir compared with subjects receiving placebo. There were no significant changes in clinical laboratory test results for those subjects who received peramivir.

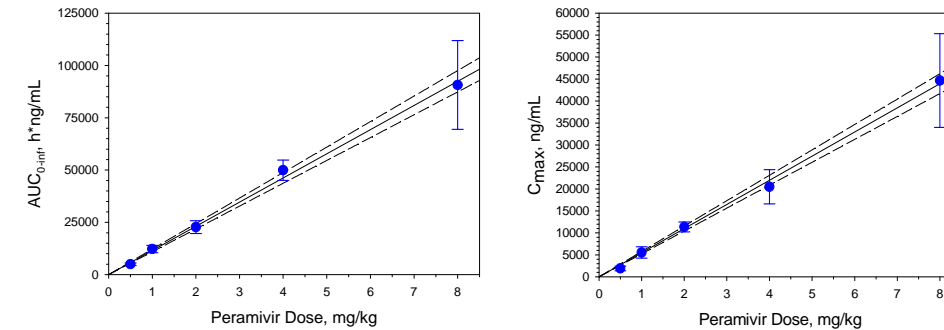
Dose (mg/kg)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-72} (h ng/mL)	$AUC_{0-\infty}$ (h ng/mL)	V_z (mL/kg)	CL (mL/h/kg)
0.5	2.9 ± 0.53	1	1925 ± 521	4995.1 ± 592.92**	4975.3 ± 593.38	426.6 ± 56.78	101.7 ± 12.04
0.5 (BID)	2.9 ± 0.83		2562 ± 368	6214.0 ± 1018.96*	6121.2 ± 784.17	283.2 ± 54.69	85.6 ± 10.25
1.0	7.7 ± 2.3	0.25	5531 ± 1292	12242 ± 1766	12246 ± 1764	910.0 ± 288.71	83.1 ± 12.5
2.0	16.3 ± 5.4	0.25	11346 ± 1120	22660 ± 3056	22689 ± 3068	1960.2 ± 772.80	83.1 ± 24.8
4.0	20.1 ± 7.1	0.25	20491 ± 3908	49809 ± 4854	49902 ± 4844	2349.7 ± 919.20	80.8 ± 7.4
8.0	20.8 ± 2.6	0.25	44666 ± 10659	90507 ± 21158	90666 ± 21203	2762.1 ± 693.50	92.8 ± 23.7
4.0 (BID)	15.9 ± 1.5		23991 ± 4758	97017 ± 15976	97890 ± 16274	1886.4 ± 422.00	81.8 ± 13.7

$t_{1/2}$ = Terminal Elimination half-life
AUC = Area Under the Curve: 0 to 12*, 0 to 48**, 0 to 72, and 0 to infinity
 V_z = Volume of Distribution
CL = Clearance

Plots of plasma concentration (ng/mL) following (A) a single intravenous infusion and (B) BID dosing.



Plots of C_{max} and $AUC_{0-\infty}$ and Peramivir Dose (mg/kg) following a single intravenous infusion.



Safety: Adverse Events

Adverse Event ¹	Single Dose Infusion		BID Dosing x 10 Days		
	Placebo (N=10)	Peramivir 0.5 to 8.0 mg/kg (N=30)	Placebo (N=9)	Peramivir 2 mg/kg (N=9)	Peramivir 4 mg/kg (N=9)
Any Adverse Event	4 (40%)	21 (70%)	8 (89%)	7 (78%)	8 (89%)
Nausea, Vomiting	0	1 (3%)	2 (22%)	0	1 (11%)
Pyrexia	1 (10%)	0	0	0	0
URTI	0	2 (7%)	1 (11%)	0	2 (22%)
Bilirubin Increased	0	2 (7%)	0	0	0
CPK Increased	0	1 (3%)	1 (11%)	0	0
ECG Qt Prolongation	0	1 (3%)	0	0	0
Hyperglycemia	1 (10%)	2 (7%)	0	0	0
Proteinuria	0	1 (3%)	0	0	0
Hematuria	0	1 (3%)	2 (22%)	2 (22%)	0
Back Pain	0	1 (3%)	0	0	0
Cystitis	0	1 (3%)	1 (11%)	0	0
Headache	1 (10%)	3 (10%)	4 (44%)	0	3 (33%)
Paresthesia	0	1 (3%)	0	1 (11%)	0
Dizziness	0	0	1 (11%)	0	0
Somnolence	0	0	0	3 (33%)	1 (11%)
Skin Irritation, Rash	1 (10%)	2 (7%)	2 (22%)	0	2 (22%)

Conclusions

This study provides important pharmacokinetic and safety data that support further development of intravenous administration in subjects with acute influenza infection. The plasma concentration of peramivir increased linearly in a dose-dependent manner with no evidence of drug accumulation. Adverse events were generally mild and self-limiting. The safety profile suggests that intravenous administration of peramivir at doses up to 8 mg/kg/day, for 1 to 10 days, may be well-tolerated.