

Neutropenia is Not Related to Neuraminidase Inhibitor (NAI) Therapy of Influenza in Phase 2 and 3 Controlled Clinical Trials

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INTRODUCTION

- Patients with influenza, including those hospitalized during the 2009/10 influenza pandemic, demonstrate rapid and pronounced lymphopenia¹⁻⁴ that usually resolves within a week.³
- Neutropenia develops more slowly than lymphopenia¹ and may be a predictor of a poor clinical outcome⁵
- Many patients with influenza are treated with neuraminidase inhibitors, but the potential influence of these therapies on peripheral blood leukocytes has not been evaluated.
- Peramivir is an intravenous neuraminidase inhibitor in Phase 3 trials in the US and approved in Japan and South Korea for treatment of influenza.
- Peramivir has been studied in over 2300 influenza patients and volunteers in a multinational development program.
- We conducted an analysis of data from five Phase 2 and 3 clinical trials to evaluate potential effects of peramivir exposure on lymphopenia and neutropenia.

METHODS

Study Designs and Treatments

Peramivir Phase 2 and 3 Clinical Trials in Adult Subjects

Study	BCX1812-211	BCX1812-212	0722T0621	0815T0631	BCX1812-201
Peramivir	150 mg IM 300 mg IM	600 mg IM	300 mg IV 600 mg IV	300 mg IV 600 mg IV	200 mg IV 400 mg IV
Control	Placebo	Placebo	Placebo	Oseltamivir 75 mg BID	Oseltamivir 75 mg BID
Treatment Duration	Single dose	Single dose	Single dose	Peramivir: Single dose Oseltamivir: 5 days	5 days
Subjects	344 outpatients	405 outpatients	300 outpatients	1099 outpatients	137 inpatients
Design	R, DB, PG	R, DB, PG	R, DB, PG	R, DB, DD, PG	R, DB, DD, PG

IV=intravenous, IM=intramuscular, R=randomized, DB=double blind, PG=parallel group, DD=double dummy

Subjects

- Enrolled subjects had
 - Positive RAT test for influenza A or B
 - Onset of acute illness 36-72 hr before presentation
 - ≥ 1 respiratory (e.g., cough) and ≥ 1 constitutional (e.g., fever) symptom
 - No recent antiviral treatment

Study Assessments

- Blood samples were drawn for determination of absolute lymphocyte counts (ALC) and absolute neutrophil counts (ANC) (cells x 10³/mm³) at screening (baseline) and approximately 48 hr and 312 hr after initiation of treatment
- An additional blood sample was drawn between 48 hr and 312 hr
- Toxicities were graded using DAIDS toxicity grading scale (2004)
- Any differences among treatment groups in change from baseline values were assessed by Wilcoxon Rank Sum Test. If differences were found, pairwise comparisons were conducted.
- The risk for neutropenia was modeled with stepwise logistic regression analysis

RESULTS

Single Dose Peramivir Studies

Number (%) of Subjects with Grade 1-4 ANC or ALC at Baseline and at 48 Hours After Single-dose Treatment with a Neuraminidase Inhibitor or Placebo

	Study 211 n=318*		Study 212 n=334*		Study 621 n=296*		Study 631 n=1049*	
	BL†	48h	BL†	48h	BL†	48h	BL†	48h
ANC‡								
Grade 1	4 (1)	22 (7)	4 (1)	17 (5)	0	35 (12)	7 (1)	104 (10)
Grade 2	1 (<1)	5 (2)	0	15 (4)	0	17 (6)	1 (<1)	63 (6)
Grade 3	0	4 (1)	0	5 (1)	0	4 (1)	0	10 (1)
Grade 4	0	0	0	1 (<1)	0	1 (<1)	0	3 (<1)
ALC‡								
Grade 1	16 (5)	0	9 (3)	0	17 (6)	0	82 (8)	2 (<1)
Grade 2	14 (4)	2 (1)	25 (7)	1 (<1)	25 (8)	0	124 (12)	0
Grade 3	15 (5)	0	26 (8)	2 (1)	35 (12)	0	156 (15)	12 (<1)
Grade 4	10 (3)	0	17 (5)	0	14 (5)	0	62 (6)	0

*Confirmed influenza cases
†BL=baseline ANC and ALC results immediately prior to administration of single-dose study treatment.
‡ANC: Grade 1 = 1000-3000 cells/mm³; Grade 2 = 750-1000 cells/mm³; Grade 3 = 500-749 cells/mm³; Grade 4 = <500 cells/mm³.
ALC: Grade 1 = 600-650 cells/mm³; Grade 2 = 500-599 cells/mm³; Grade 3 = 350-499 cells/mm³; Grade 4 = <350 cells/mm³.

- Across 4 trials, graded neutropenia was uncommon at baseline, with only 17/1997 (0.9%) subjects having ANC <3000 cells/mm³ (Grades 1 and 2) and no subjects <750 cells/mm³ (Grades 3 and 4)
- Neutropenia incidence increased by 48 hours to 306/1997 (15%) subjects, with 28/1997 (1.4%) subjects experiencing a Grade 3 or 4 reduction in neutrophils across the 4 trials
- Graded lymphopenia was present in 647/1997 (32.4%) subjects; 103/1997 (5.2%) of subjects had Grade 4.
- By 48 hr, graded lymphopenia was present in only 19/1997 subjects (1%).

ALC in Placebo-Controlled Studies of Peramivir

Study		Screening	48 hr	Change	
Study 211	Peramivir 300 mg (n=105)	Median (Min, Max)	0.90 (0.32, 5.23)	1.82 (0.22, 3.67)	+ 0.80 (-1.11, 2.13)
	Peramivir 150 mg (n=104)	Median (Min, Max)	1.03 (0.32, 5.23)	1.83 (0.73, 5.33)	+ 0.78 (-0.72, 2.39)
	Placebo (n=109)	Median (Min, Max)	1.01 (0.15, 3.27)	1.46 (0.58, 3.08)	+ 0.47 (-0.72, 1.90)
Overall P<0.001; 300 mg vs placebo P<0.001; 150 mg vs placebo P<0.001; 300 mg vs 150 mg P=0.99					
Study 212	Peramivir 600 mg (n=160)	Median (Min, Max)	1.01 (0.14, 4.43)	1.60 (0.49, 5.03)	+ 0.60 (-0.96, 1.92)
	Placebo (n=174)	Median (Min, Max)	0.92 (0.13, 4.97)	1.49 (0.44, 4.68)	+ 0.52 (-1.11, 2.84)
	Overall P=0.629; 600 mg vs placebo P=0.629				
Study 621	Peramivir 600 mg (n=97)	Median (Min, Max)	0.83 (0.19, 2.70)	1.55 (0.82, 3.07)	+ 0.71 (-0.68, 2.11)
	Peramivir 300 mg (n=99)	Median (Min, Max)	0.85 (0.31, 1.92)	1.46 (0.72, 3.02)	+ 0.61 (-0.34, 1.68)
	Placebo (n=100)	Median (Min, Max)	0.77 (0.23, 1.83)	1.28 (0.60, 3.13)	+ 0.52 (-0.49, 1.66)
Overall P=0.003; 600 mg vs placebo P<0.001; 300 mg vs placebo P=0.019; 600 mg vs 300 mg P=0.250					

- Lymphocyte counts 48 hr post-treatment demonstrated significantly greater increases from baseline with both doses of peramivir in Study 211 (150 and 300 mg IM) and Study 621 (300 and 600 mg IV) compared with placebo

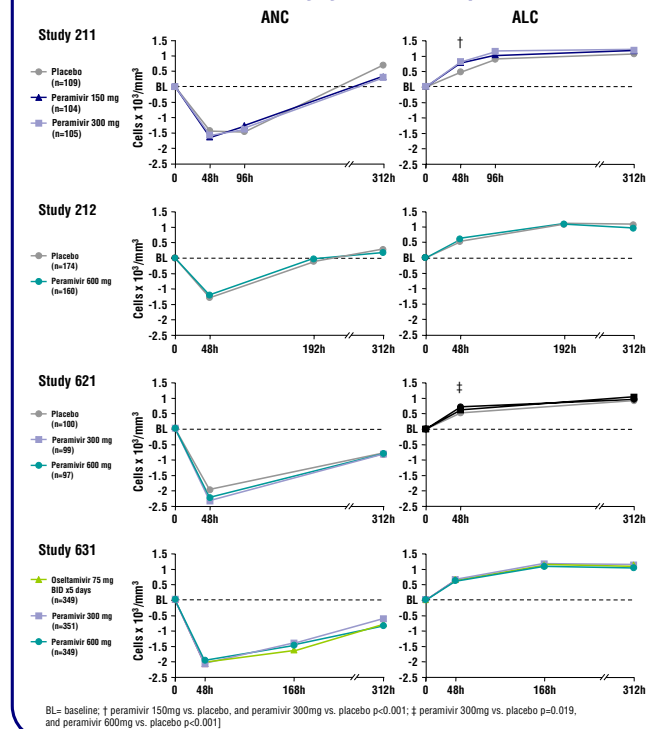
Multiple Dose Peramivir Study (201)

Number (%) of Subjects* with Grade 1-4 ANC or ALC at Baseline and Post-Treatment in Study 201

	ANC		ALC	
	Baseline†	Post-Treatment‡	Baseline†	Post-Treatment‡
Grade 1	0	8 (6%)	10 (7%)	0
Grade 2	0	4 (3%)	8 (6%)	1 (1%)
Grade 3	0	0	11 (8%)	2 (1%)
Grade 4	0	2 (1%)	5 (4%)	2 (1%)
Total 1-4	0	14 (10%)	34 (25%)	5 (4%)

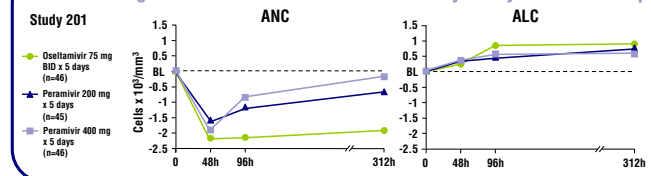
*Only subjects with an increase of ≥ 1 grade from baseline value; if subject experienced laboratory toxicity > once, only the greatest severity is presented
†Results immediately prior to administration of first dose
‡Following initiation of study treatment up to 14 days after discontinuation

Median Changes from Baseline in ANC and ALC at Intervals in Each Study by Treatment Group



BL= baseline; † peramivir 150mg vs. placebo, and peramivir 300mg vs. placebo p<0.001; ‡ peramivir 300mg vs. placebo p=0.019, and peramivir 600mg vs. placebo p<0.001

Median Changes from Baseline in ANC and ALC in Study 201 by Treatment Group



Predictors of Neutropenia

Risk Factors for Treatment Emergent Grade 2, 3, or 4 Neutropenia* in Combined Peramivir Studies†

Parameter	Neutropenia Present (n=165)	Neutropenia Absent (n=1954)	Odds Ratio (95% CI)	P value
Baseline WBC Count, 10 ⁹ /UL, median	4.19	5.81	0.46 (0.40, 0.54)†	<0.001
Race (Black vs White), n (%)	18 (11%) vs 21 (13%)	133 (7%) vs 452 (23%)	4.36 (2.10, 9.06)	<0.001
Age, yr, mean (SD)	32 (10.2)	37 (14.0)	0.97 (0.95, 0.98)†	<0.001
Baseline Lymphocyte Count, 10 ⁹ /UL, median	0.66	0.83	0.50 (0.30, 0.83)†	0.008
Race (Asian vs White), n (%)	123 (75%) vs 21 (13%)	1304 (67%) vs 452 (23%)	1.79 (1.07, 3.00)	0.026

*Neutropenia at any timepoint following initiation of study treatment and increased by ≥ 1 grade from baseline toxicity level
†BCX1812-201, BCX1812-211, BCX1812-212, 0722T0621, 0815T0631
‡Decrease in odds relative to 1 unit increase in the variable

- The risk for neutropenia was increased in those subjects who
 - had lower baseline WBC counts
 - were black or Asian
 - were younger
 - had lower baseline lymphocyte counts
- Predictors that did not significantly increase the risk for neutropenia were
 - peramivir treatment
 - oseltamivir treatment
 - gender
 - baseline TCID₅₀
 - influenza strain
 - influenza season
 - time from symptom onset to enrollment (<48 hr vs ≥48 hr)
 - baseline neutrophil count

DISCUSSION

- As previously described¹⁻⁵, this analysis demonstrated that early lymphopenia is followed by neutropenia in subjects with influenza
- Over the course of these 5 clinical trials, lymphocyte counts increased and neutrophil counts decreased and recovered irrespective of treatment with NAIs or placebo
- Risk factors for neutropenia included low baseline WBCs, race (black or Asian), younger age, and low baseline lymphocytes but not NAI treatment
- Improvements in lymphopenia occurred more rapidly with peramivir treatment than with placebo in 2 of the 3 placebo-controlled trials, which may reflect a treatment effect and early antiviral control of infection
- Delayed neutropenia in human influenza is less well known than the early lymphopenia, perhaps because of the lack of rigorous follow up in most influenza cases or studies

CONCLUSIONS

- Early lymphopenia, sometimes striking, is common in acute influenza and a risk factor for emergent neutropenia.
- Later decreases in neutrophil counts are part of the pathophysiology of influenza and not a result of treatment with peramivir or oral oseltamivir.
- Peramivir has no apparent effects on leukocyte counts, lymphocyte counts or risk of neutropenia in patients with influenza.

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