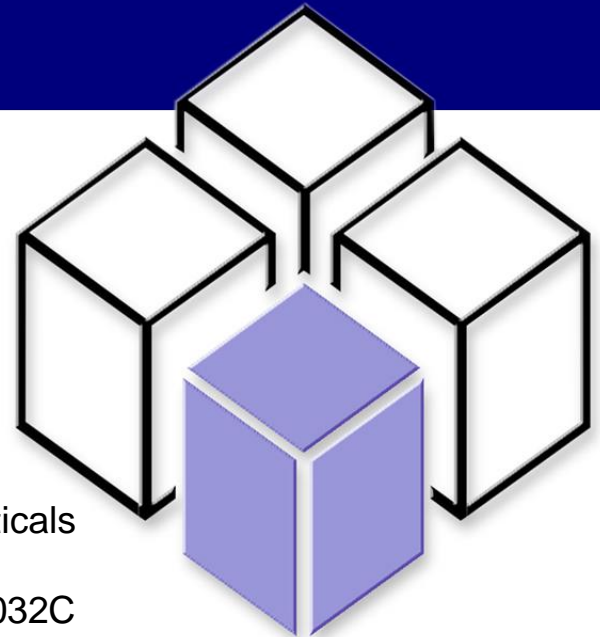


Safety and Antiviral Effect of Multi-Day Therapy with IV Peramivir 300mg BID or 600mg QD in Hospitalized Influenza Subjects

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Background

- > 200,000 people are hospitalized and > 30,000 die with seasonal influenza annually in the US
- In the 2009 influenza A(H1N1) pandemic, the rates of hospitalization and death significantly increased in children and working adults
- Many hospitalized with influenza require intensive care
- There is no approved parenteral product for hospitalized patients in the US
- Currently available oral/inhaled products may not be ideal
- Anti influenza drug resistance may compromise therapy
- New antivirals, particularly IV antivirals, are needed to treat influenza

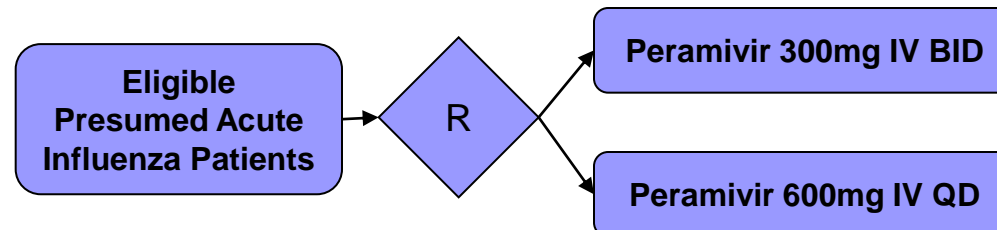


Objectives

- Few studies have focused on patients hospitalized with influenza
- We conducted a study during the 2009 pandemic to evaluate the safety and antiviral effect of multi-day therapy with IV peramivir, an investigational NAI, in hospitalized subjects with influenza

BCX1812-303 Study Design Summary

- Open-Label, Randomized, multicenter study
- Broad eligibility criteria, no restriction on prior use of NAIs or illness duration
- Sample size ~300 subjects
- Powered to detect time-weighted change from baseline to 48-hours in influenza viral titer using a two-sided test with 95% confidence interval when a width of the confidence interval is less than 0.24 (using $\log_{10} \text{TCID}_{50}$)
- Primary Endpoint
 - Change (reduction) in influenza virus titer measured by \log_{10} tissue culture infective dose (TCID_{50})
- Stratified enrollment according to duration of illness:
 - ≤ 48 hrs
 - > 48 hrs
- Interventions
 - Peramivir
 - 300mg IV BID compared to 600mg IV QD



BCX1812-303 Study Population Disposition

Peramivir 300 mg BID

Peramivir 600 mg QD

Subjects Enrolled

Intent to Treat (ITT) Population:
n = 234

Randomized Not Treated: n = 4

Safety Population:
n = 230

Withdrawals
n = 50

Completed Study: n = 180

n = 234

n = 117

n = 2

n = 115

n = 24

Adverse Event = 2
Lost to Follow-Up = 4
Withdrew Consent = 9
Death = 4
Other = 4
Missing = 1

n = 91

n = 117

n = 2

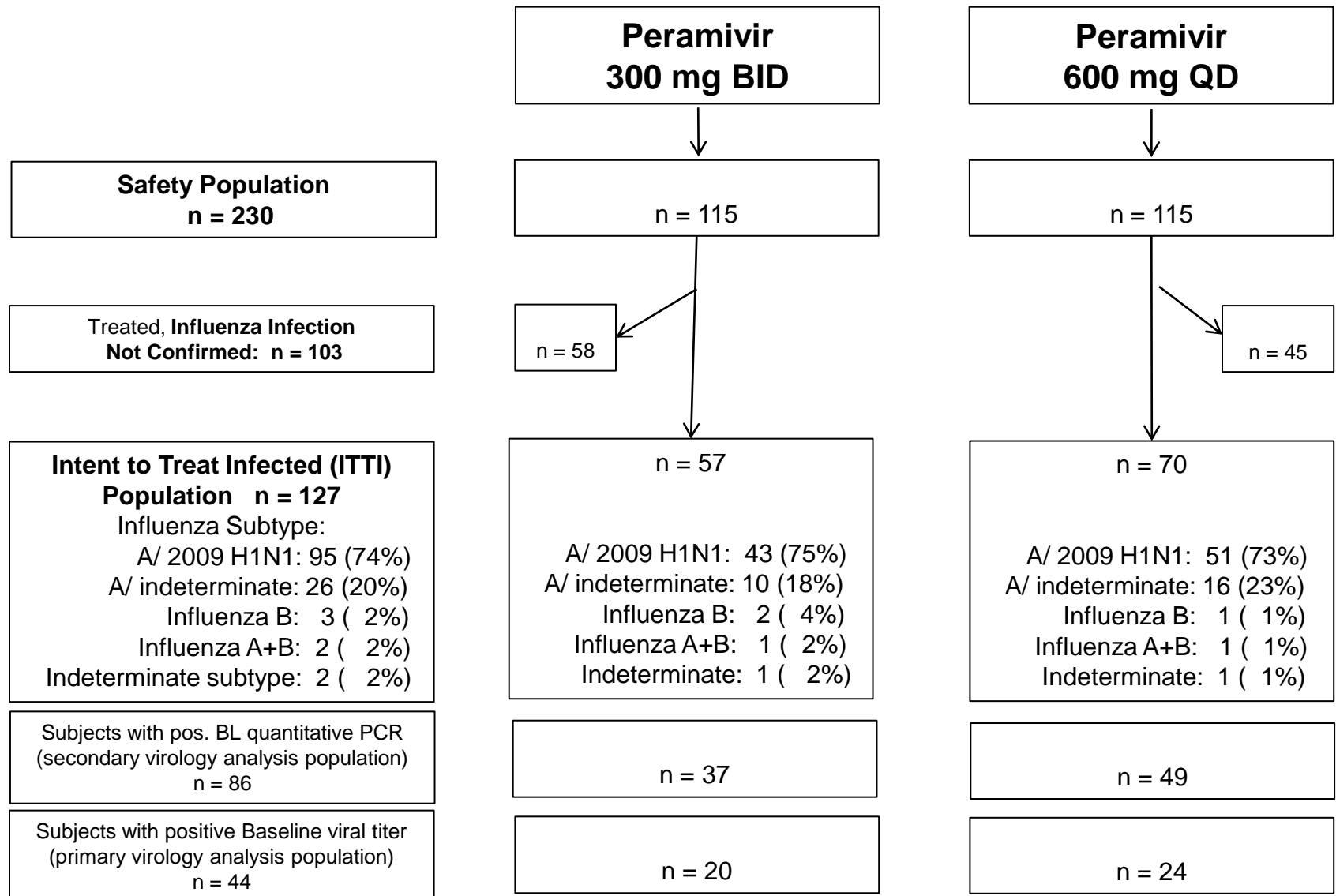
n = 115

n = 26

Adverse Event = 1
Influ. – Related Comp. = 1
Investigator Discretion = 1
Lost to Follow-Up = 7
Withdrew Consent = 2
Death = 10
Other = 4

n = 89

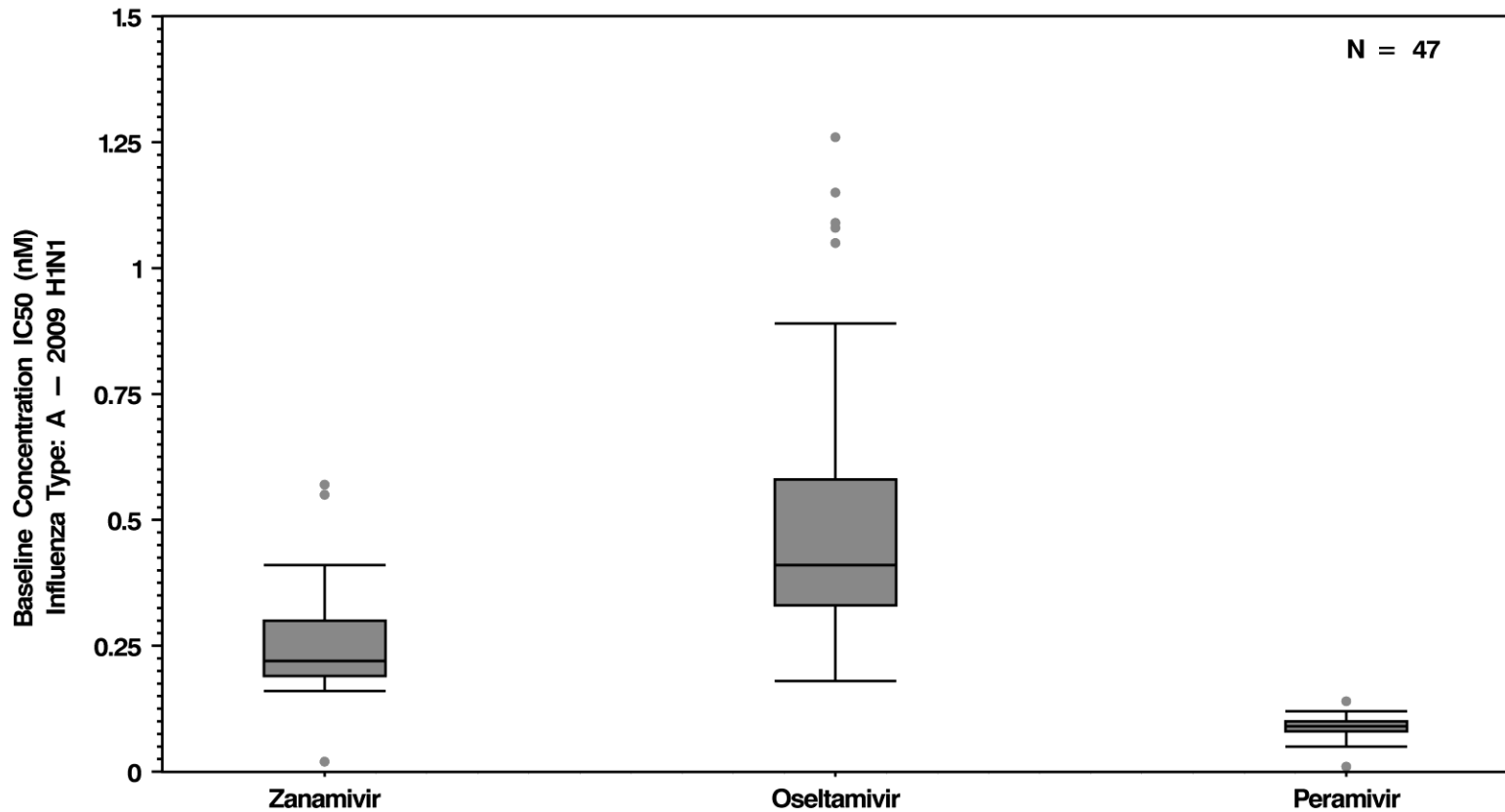
BCX1812-303 Virology Population Disposition



Study BCX1812-303 - Demographics– ITTI

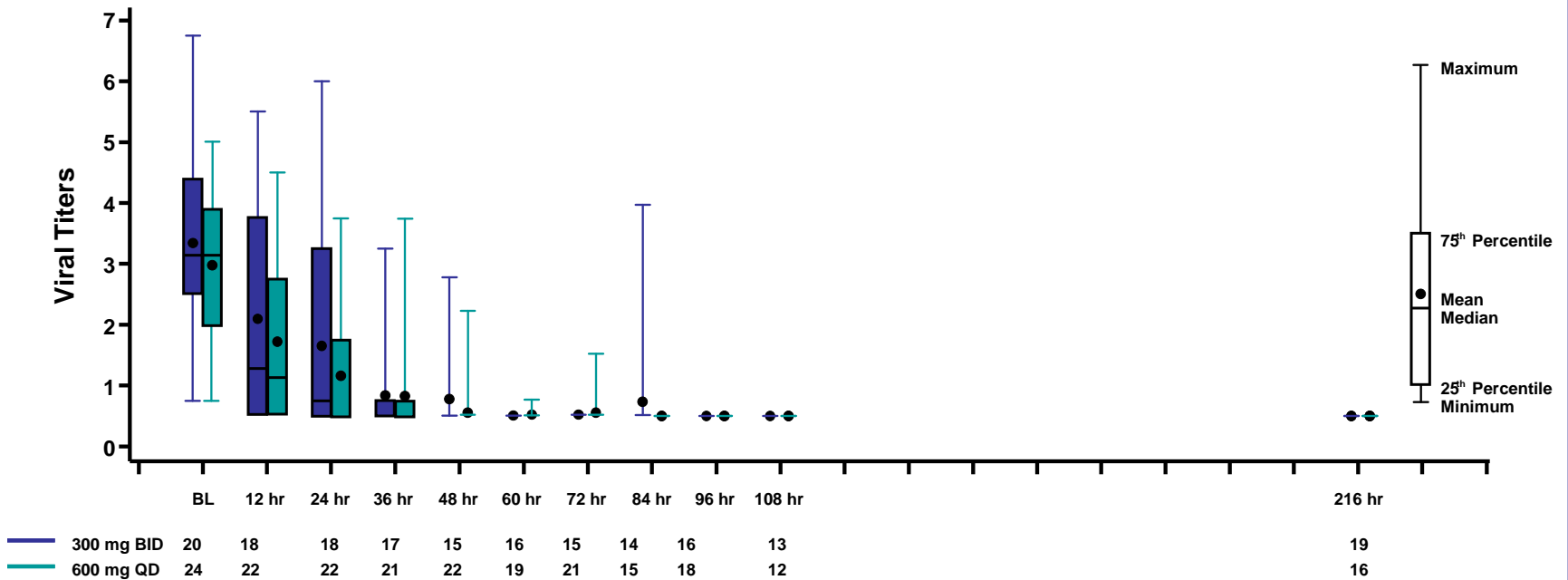
Parameter	Peramivir 300 mg BID n = 57	Peramivir 600mg QD n = 70
Age, median (min, max) Adolescents (12-17)	45.4 (14.3, 92.5) 1	46.3 (18.9, 88.1) 0
Gender: male female	21 (37%) 36 (63%)	39 (56%) 31 (44%)
BMI (kg/m ²), median (min, max)	30.1 (16.8, 70.1)	29.5 (18.1, 55.7)
Smoking status: currently a smoker Does not currently smoke	20 (35%) 37 (65%)	27 (39%) 43 (61%)
Vaccination status: Not vaccinated this year Vaccinated this year	35 (61%) 22 (39%)	50 (71%) 20 (29%)
Duration of illness: ≤ 48 hr > 48 hr	10 (18%) 47 (82%)	12 (17%) 58 (83%)
# of subjects requiring supplemental O ₂ at baseline	35 (61%)	52 (74%)
# of subjects with ICU admission at baseline	9 (16%)	15 (21%)
Prior antiviral therapy	47 (82%)	53 (76%)
APACHE II score, median (min, max) (for first ICU admission)	n = 8 12 (4, 28)	n = 12 16 (9, 28)

Baseline susceptibility of isolated influenza viruses



Primary Efficacy Analysis: Similar reductions in viral titer between treatment groups

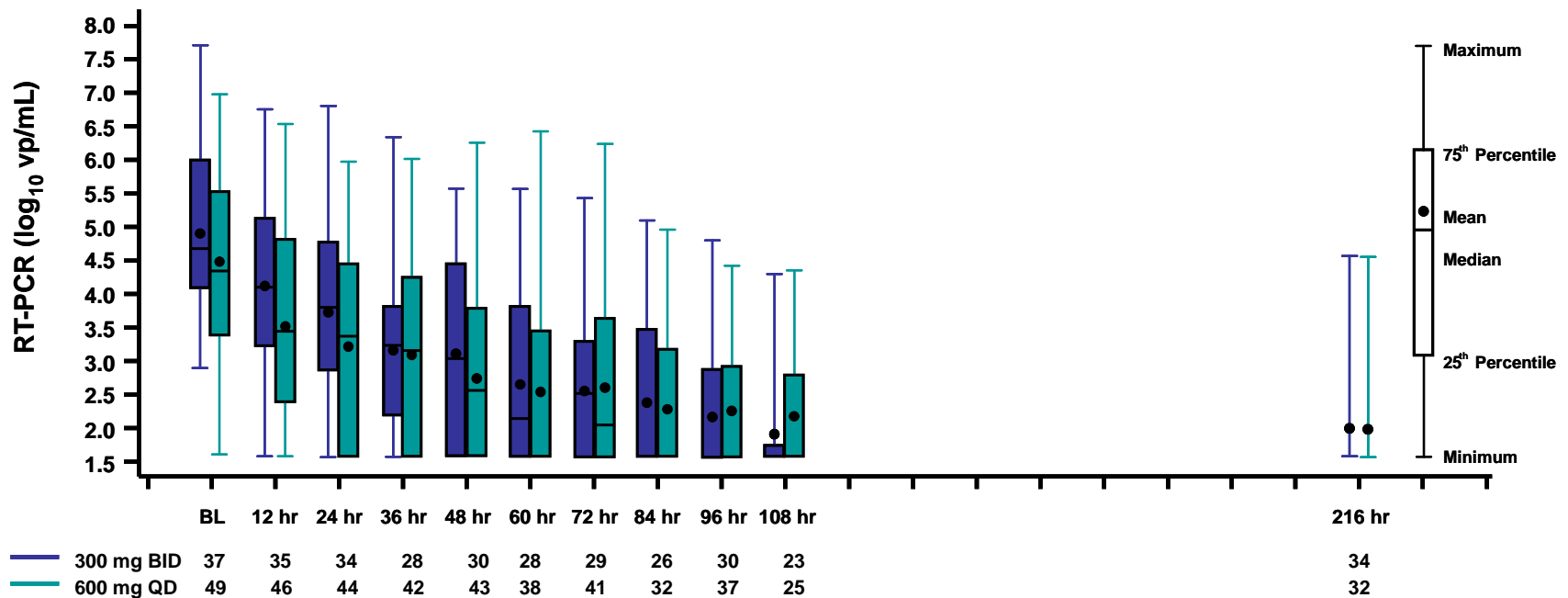
TW Change: BL to 48 hrs	Peramivir 300mg BID	Peramivir 600mg QD
N	20	24
Median (95% CI)	-1.66 (-2.32,-0.61)	-1.47 (-1.89, -0.75)
Min, Max	-3.55, -0.09	-3.37, -0.20



Note: Negative viral titer by culture is a $\log_{10} \text{TCID}_{50}/\text{mL} = 0.5$

Secondary Virology Analysis: Similar reductions in PCR titer between treatment groups

TW Change: BL to 48 hrs	Peramivir 300mg BID	Peramivir 600mg QD
N	37	49
Median (95% CI)	-1.00 (-1.52,-0.77)	-1.07 (-1.24, -0.67)
Min, Max	-2.52, 1.10	-2.49, 0.25



Note: Negative PCR is \log_{10} vp/mL of 1.58 for influenza A and 1.49 for influenza B.

Secondary Virology Analysis: Little Change in 2009 H1N1 influenza A virus susceptibility to NAIs, median IC₅₀ nM – ITTI

Treatment Group	Peramivir	Oseltamivir	Zanamivir
Peramivir 300 BID			
Baseline, Mdn (min,max)	0.09 (0.01, 0.14)	0.37 (0.32, 1.15)	0.22 (0.16, 0.55)
Last +, Mdn (min,max)	0.09 (0.06, 31.02)	0.37 (0.23, 282.4)	0.23 (0.08, 0.30)
Median Fold Change	No change*	No change*	No change
Peramivir 600 QD			
Baseline, Mdn (min,max)	0.09 (0.05, 0.14)	0.43 (0.18, 1.26)	0.22 (0.02, 0.57)
Last +, Mdn (min,max)	0.10 (0.07, 0.13)	0.38 (0.28, 0.93)	0.25 (0.11, 0.34)
Median Fold Change	No change	No change	No change

Two genotyping (GT) subsets were defined: paired isolates with NAI IC₅₀s > BL mean + 2 SD and subjects culture positive at day 5. ***Only one isolate (high post-BL IC₅₀) had H275Y**

Summary of secondary clinical endpoints – ITTI

Analyses stratified by important baseline factors

Parameter	Peramivir 300 BID	Peramivir 600 QD
TTCR, Overall ITTI, Hrs Median (95% CI) n=126	n=56 44.7 (40.7, 118.5)	n=70 166.1 (84.0, 273.1)
TTCR, Suppl. O ₂ required at BL, Hrs Median (95% CI) n=87	n=35 165.9 (65.6, NA)	n=52 177.0 (115.9, 283.2)
TTCR, No suppl. O ₂ required at BL, Hrs Median (95% CI) n=39	n=21 29.1 (18.8, 42.2)	n=18 20.1 (12.4, 173.0)
TTCR, In ICU, (all required suppl. O ₂ at BL), Hrs Median (95% CI) n=24	n=9 NA	n=15 283.2 (114.6, 283.2)
TTCR, Not in ICU, Hrs Median (95% CI) n=102	n=47 43.0 (28.8, 66.0)	n=55 115.9 (46.3, 190.3)
TTCR, Not in ICU, suppl. O ₂ required at BL, Hrs Median (95% CI) n=63	n=26 103.5 (44.7, 203.0)	n=37 166.3 (92.0, 277.6)
TTCR, Not in ICU, No suppl. O ₂ required at BL, Hrs Median (95% CI) n=39	n=21 29.1 (18.8, 42.2)	n=18 20.1 (12.4, 173.0)
Predictors of TTCR in multivariable logistic regression: Supplemental Oxygen required at BL: HR(95%CI): 2.42 (1.47, 3.99), p<0.001. Need for ICU care: HR(95%CI): 3.15 (1.32, 7.55), p=0.01.		

Other secondary clinical endpoints – ITTI

Parameter	Peramivir 300 mg BID	Peramivir 600mg QD
Time To Resumption of Usual Activities Days, Median (95% CI), n= 112	n=53 27.7 (17.8, NA)	n=59 24.9 (13.5, 28.8)
Time To Hosp Discharge Days, Median (95% CI), n=127	n=57 6.0 (5.0,8.0)	n=70 6.0 (6.0, 11.0)
Time To Alleviation of Symptoms Hours, Median (95% CI), n=109	n=51 135.1 (89.0, 184.0)	n=58 158.4 (103.1, 305.5)
14 Day survival n=127	n=57 98%	n=70 93%
28 Day survival n=127	n=57 94%	n=70 86%

Study BCX1812-303 – Most common Adverse Events – Safety Population

Adverse Event	Peramivir 300 mg BID n = 114	Peramivir 600mg QD n = 116	Total N=230
ANY ADVERSE EVENT	90 (79%)	85 (73%)	175 (76%)
Mild	31 (27%)	20 (17%)	51 (22%)
Moderate	28 (25%)	27 (23%)	55 (24%)
GI DISORDERS	41 (36%)	45 (39%)	86 (37%)
Constipation	19 (17%)	11 (9%)	30 (13%)
Diarrhea	13 (11%)	16 (14%)	29 (13%)
Nausea	10 (9%)	8 (7%)	18 (8%)
RESPIRATORY DISORDERS	32 (28%)	30 (26%)	62 (27%)
Respiratory Failure	5 (4%)	4 (3%)	9 (4%)
METABOLISM DISORDERS	24 (21%)	35 (30%)	59 (26%)
Hypokalemia	8 (7%)	14 (12%)	22 (10%)
INFECTIONS AND INFESTATIONS	30 (26%)	27 (23%)	57 (25%)
Urinary Tract Infection	1 (1%)	1 (1%)	2 (1%)
GENERAL DISORDERS	25 (22%)	21 (18%)	46 (20%)
Edema Peripheral	10 (9%)	8 (7%)	18 (8%)
BLOOD AND LYMPHATIC DISORDERS	9 (8%)	17 (15%)	26 (11%)
Anemia	5 (4%)	13 (11%)	18 (8%)

Serious adverse event summary, safety population

- Overall rate of SAEs was 20%. The most common System Organ Classes with SAEs were:
 - Respiratory 9%
 - Infections 8%
 - Renal 3%
 - Cardiac 2%
 - Vascular disorders 2%
- The most common individual SAEs reported were:
 - Respiratory failure 3%
 - ARDS 2%
 - Septic Shock 2%
 - Acute renal failure 2%
 - All the rest were $\leq 1\%$ and usually single reports
- Looking at some composites of similar medical concepts:
 - Pneumonia (reported as pneumonia, bacterial pneumonia, staphylococcal pneumonia, lower respiratory tract infection, and necrotizing pneumonia) was 3% although each individual event was $\leq 1\%$
 - Renal failure (reported as renal failure and renal failure acute) remained 2%
 - Respiratory insufficiency (reported as respiratory failure, acute respiratory failure, respiratory distress) was 4%

28-day mortality stratified analyses

Subgroup	300mg BID	600mg QD	P between treatment group*
Supplemental oxygen at study entry (n=158)	7/74 (9%)	12/84 (14%)	0.490
No supplemental oxygen at study entry (n=72)	1/40 (3%)	0/32 (0%)	
ICU at study entry (n=39)	1/18 (6%)	5/21 (24%)	0.397
No ICU at study entry (n=191)	7/96 (7%)	7/95 (7%)	

* P-value is based on a Cochran-Mantel-Haenszel General Association statistic controlling for condition (ICU admission or supplemental oxygen use).

Effect of need for supplemental oxygen at study entry: $p = 0.008^{**}$

Effect of need for ICU admission at study entry: $p = 0.104^{**}$

** P-value is based on a Chi-square statistic comparing mortality and condition regardless of treatment group.

BCX1812-303: Conclusions

- Study 303 is one of the largest, prospective studies of an influenza antiviral in the hospital setting completed to date
- The 2 dose regimens of IV peramivir studied were generally safe and well tolerated
- The number of subjects contributing to the primary virology endpoint was small
- No significant differences were observed in the primary or secondary virology endpoints studied
- No observed changes in viral susceptibility to NAIs following peramivir treatment
- The observed clinical differences are likely due to imbalances in a number of baseline predictors identified from a multivariable analysis and stratified analyses
 - The most important of these are baseline need for supplemental oxygen and baseline ICU admission

BCX1812-303: Conclusions

- The average severity of illness was much worse than in study BCX1812-201. This is likely due to a combination of:
 - The greater burden of disease seen with the pandemic viral strain compared to seasonal strains prevalent for study BCX1812-201
 - Inclusion of patients who had previously been treated with oseltamivir, which tends to select for more seriously ill patients
 - Inclusion of patients needing ICU care and no restriction on duration of illness or hospitalization at study entry.
- Mortality at 28 days in this study is similar to the rate reported by FDA in their peramivir EUA Medwatch safety analyses presented at ICAAC 2010.
- The time to clear 2009 H1N1 virus was longer than was observed in BCX1812-201, confirming other reports of the viral dynamics of this virus