



Update on IV Peramivir Phase 3 Trials

Michael G. Ison, MD MS

Divisions of Infectious Diseases &
Organ Transplantation
Transplant Infectious Diseases Service
Northwestern University
Comprehensive Transplant Center

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Disclosures

- Research Support[°]
 - ADMA, Adamas, BioCryst*, Chimerix, GlaxoSmithKline, Roche, ViraCor
- Paid Consultation
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- Data & Safety Monitoring Board Participation
 - Chimerix, NexBio
- Role of BioCryst with Development of Presentation
 - Provided data and reviewed content of presentation



Update on IV Peramivir Phase 3 Trials

- Background & Challenges
 - Key features of IV peramivir
 - Unique features and basic science
 - Susceptibility and Pharmacokinetics
- Completed Phase 1 & 2 Studies
- Available data from pandemic treatment
- Phase 3 Studies
 - Asian studies leading to licensure in Japan & South Korea
 - ROW Studies
 - BCX1812-303: Completed
 - BCX1812-301: Ongoing
- Conclusions

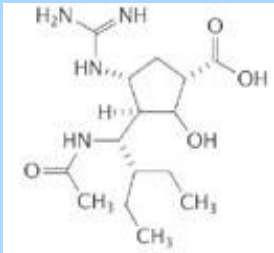
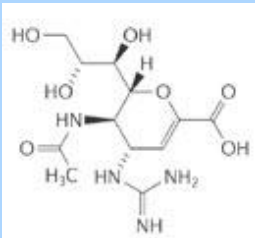
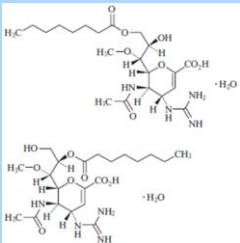
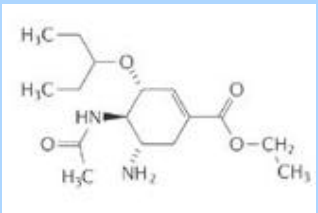


Challenges to Studying

- Clinical outcomes are not validated
- Variation of indications for hospitalization across sites
- Poor recognition of influenza among hospitalized patients
- Recruitment hurdles
 - Small numbers
 - Geographic variation in disease
 - Obtaining consent from impaired/intubated patients
- Disease pathogenesis, clinical course, and prognosis are affected by:
 - Age of the patient
 - Co-morbidities
 - Type/subtype of virus
 - Time to presentation for care
 - Immunologic status
 - Reasons for admission
 - Antiviral susceptibility
- Most patients, subjects and their guardians are unwilling to participate in placebo-controlled studies for ethical reasons

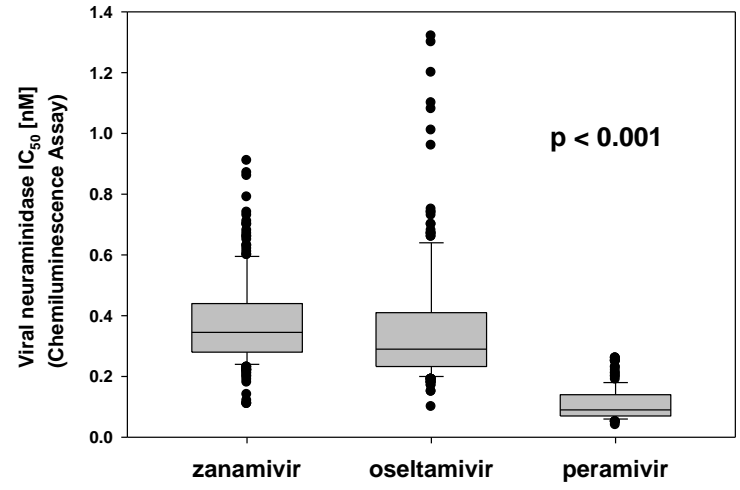


Available & Investigational NAIs

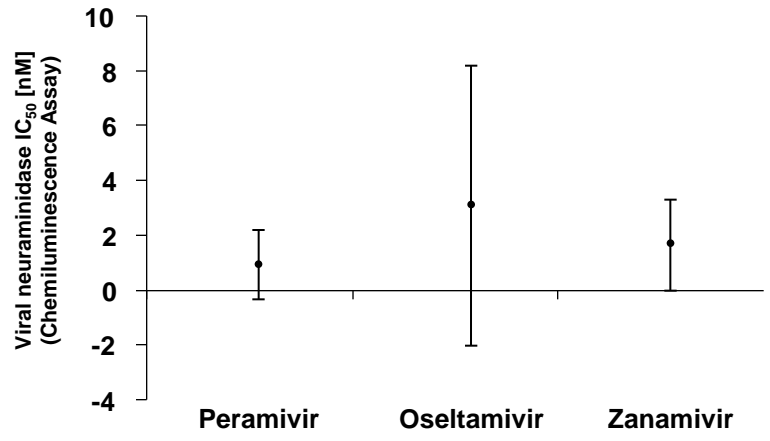
	Peramivir	Zanamivir (Relenza®)	Laninamivir	Oseltamivir (Tamiflu®)
Structure:				
Half life of drug – neuraminidase complex	> 24 hours	1.25 hours	N/A	1.25 hours
Route of administration	Parenteral	Inhaled	Inhaled	Oral

In vitro Susceptibility Data: Oseltamivir, Peramivir, & Zanamivir

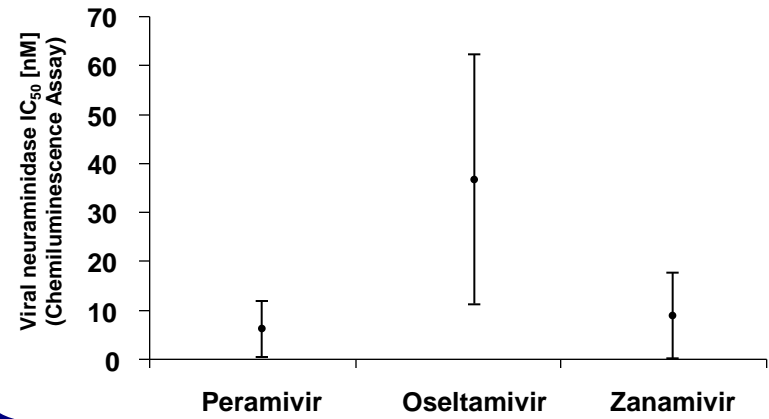
Influenza A/pH1N1 n = 204



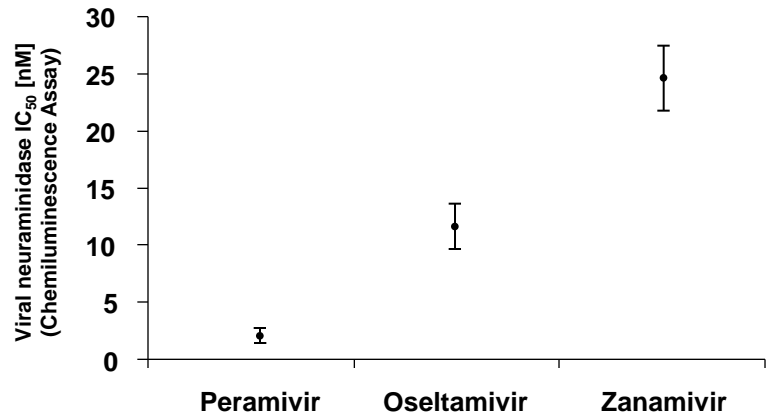
A/H3N2 n = 59



Influenza B n = 32



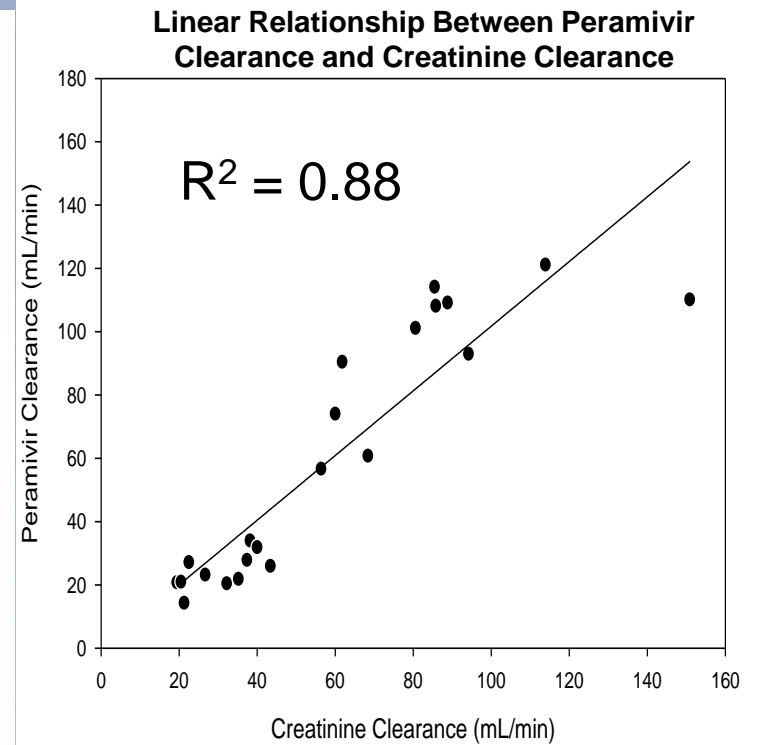
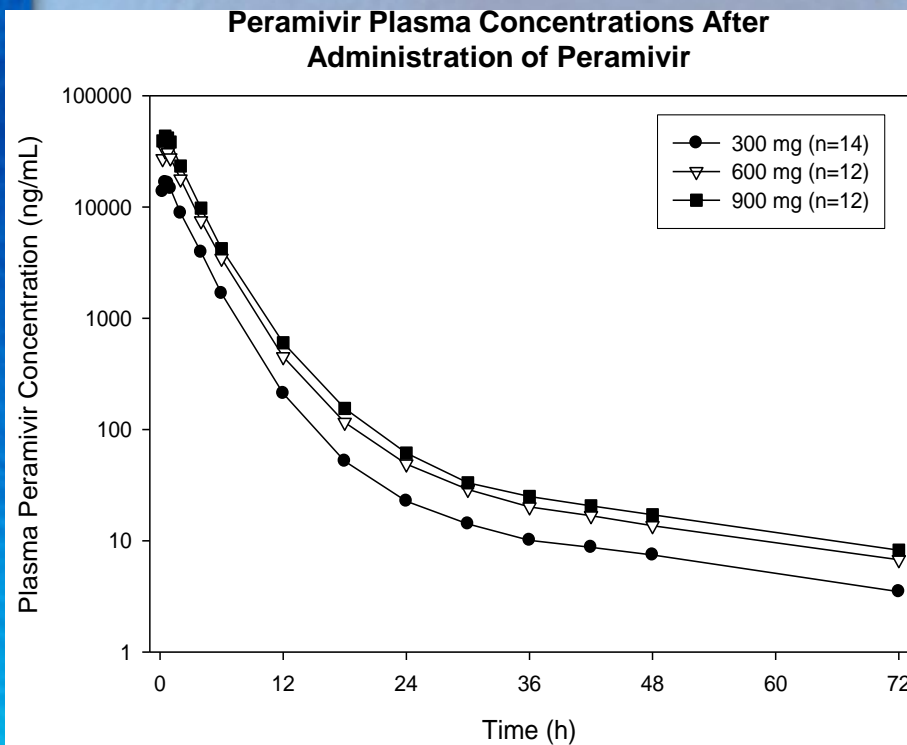
Avian influenza A Viruses n = 9



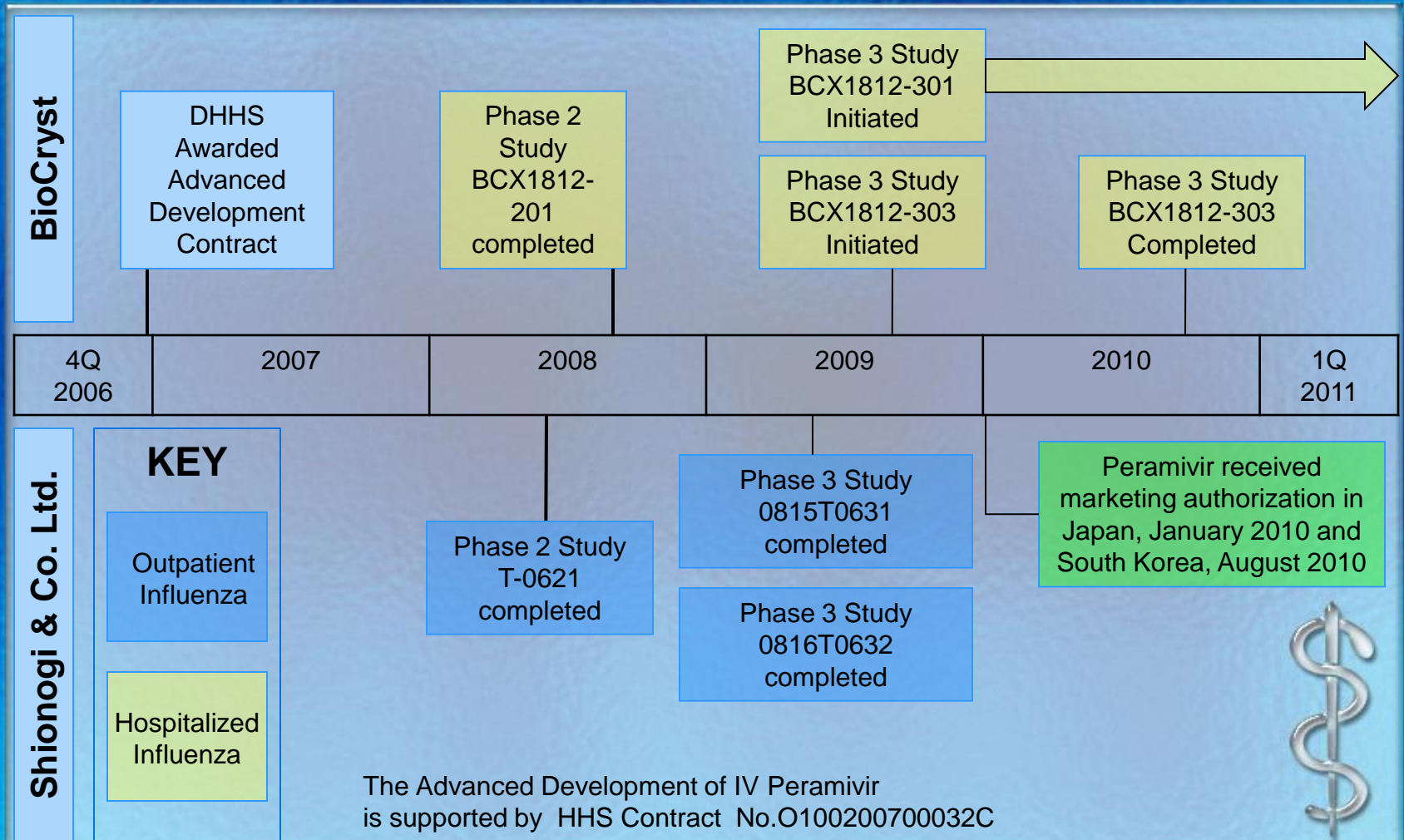
Boivin *et al.* **Antiviral Res.** 2002; 54 : 143-147. Gubareva *et al.* **AAC.** 2002; 45 : 3403-08. Bantia *et al.* **AAC.** 2001; 45 : 1162-67. Goborkova *et al.* **AAC.** 2002; 45 : 2723-32. BCX1812-201

Peramivir Pharmacokinetics

Clinical PK Parameter	Peramivir 600mg i.v.
C_{max} , mean (SD)	44,666 (10,659) ng/mL
$AUC_{0-\infty}$, mean (SD)	90,666 (21,203) ng·hr/mL



IV Peramivir Clinical Development



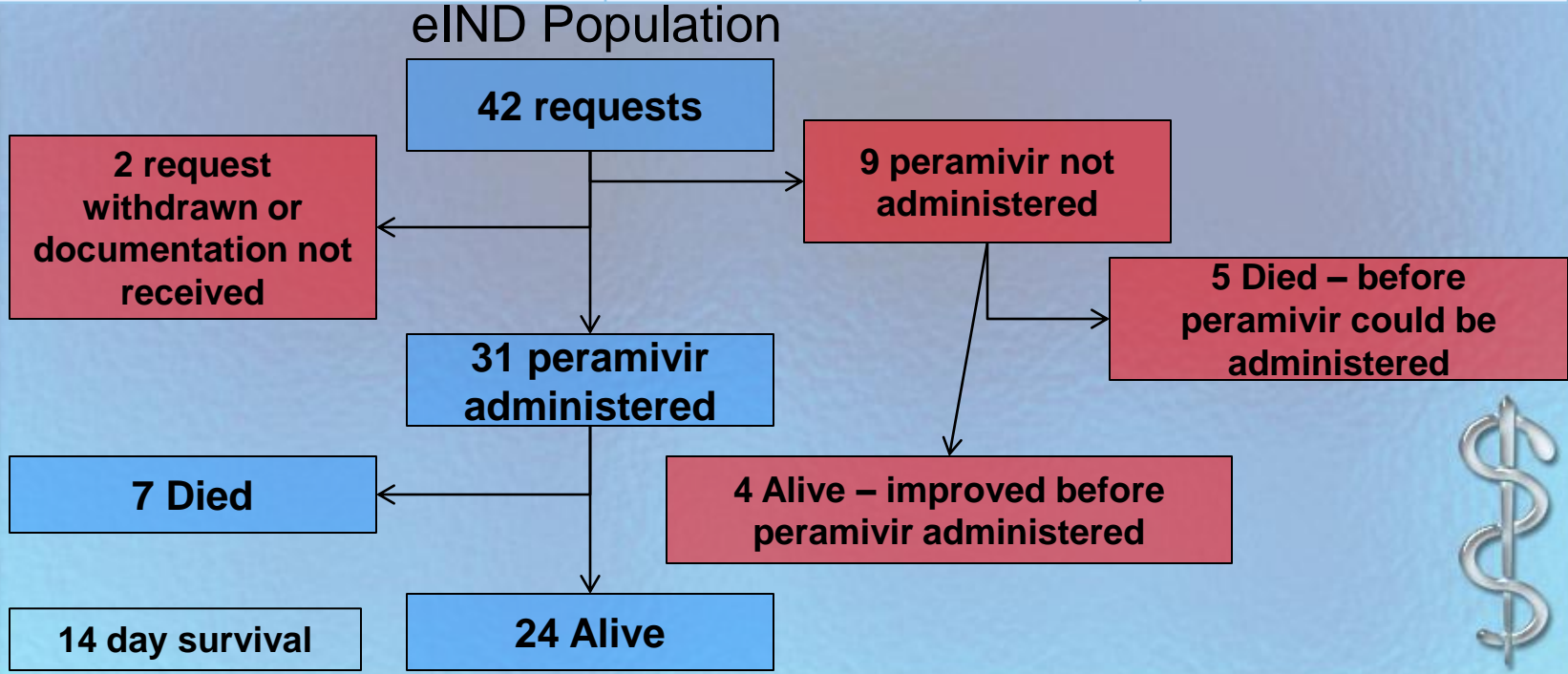
Over 2,400 subjects have received parenteral peramivir in controlled clinical trials to date

	Number of Subjects Exposed to Peramivir	Dose range
Phase I: IV		
Single dose	178	0.5 mg/Kg - 1200 mg
Multiple dose (1-10 days)	73	2 mg/Kg – 400 mg
Phase I: IM		
Single dose	175	75 – 900 mg
Multiple dose (2 days)	18	75 – 300 mg
Phase 2: IV		
Single Dose	198	300 - 600 mg
Multiple dose (5 days)	91	200 – 400 mg
Phase 2/3: IM		
Single dose	485	150 – 600 mg
Phase 3: IV		
Single Dose	843	300 – 600 mg
Multiple Dose (2-5 days)	377	300 – 600 mg
Total Subject Numbers:	2438	



Use of IV Peramivir in the US during the 2009/10 Pandemic

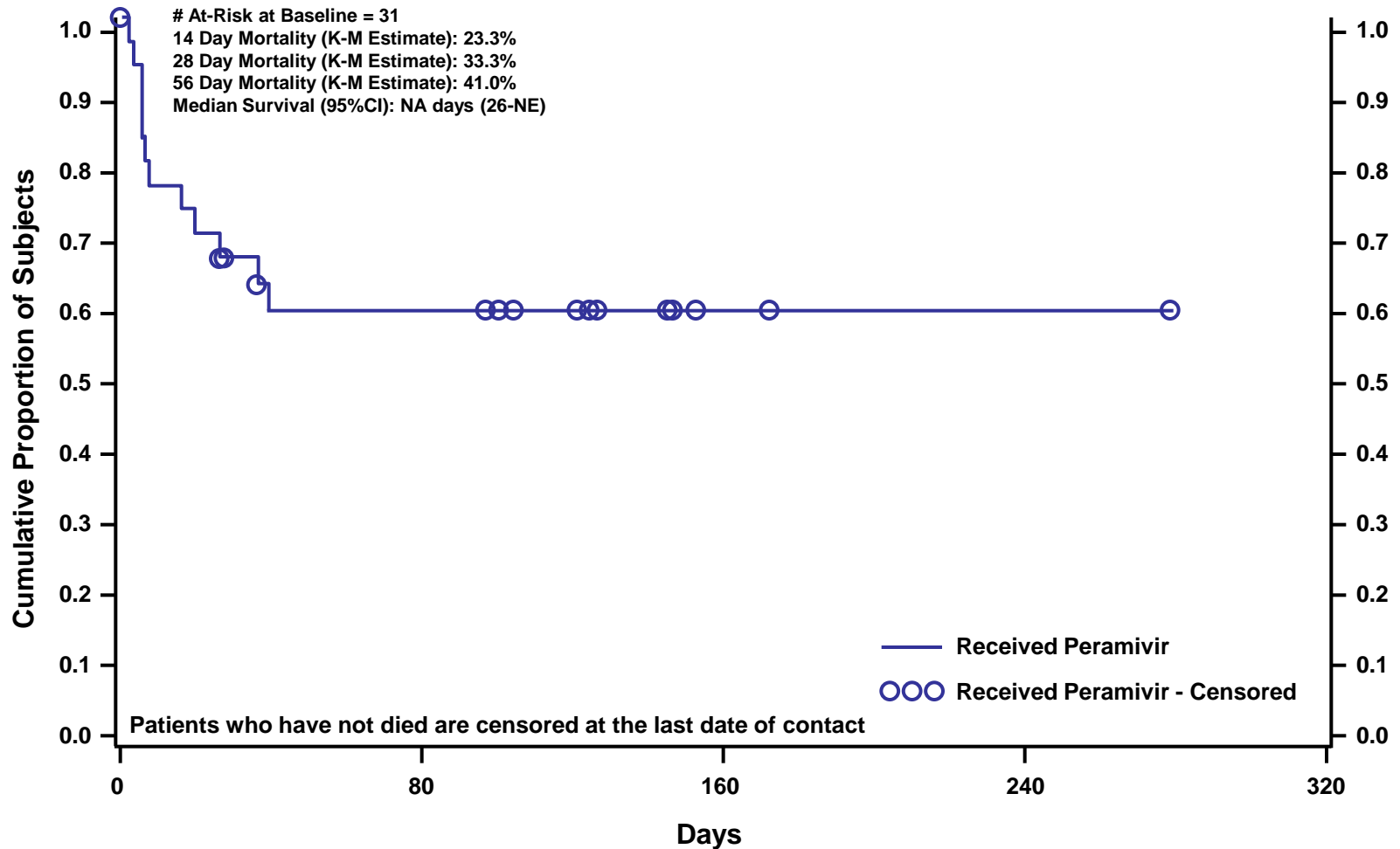
Period	Number of Subjects	Dose regimen
Individual emergency IND requests (May – Oct 2009)	31	600 mg / day 5-14 days
FDA Emergency Use Authorization (EUA) Oct 2009 - Jun 2010 *	1,371	600 mg / day 5 -10 days



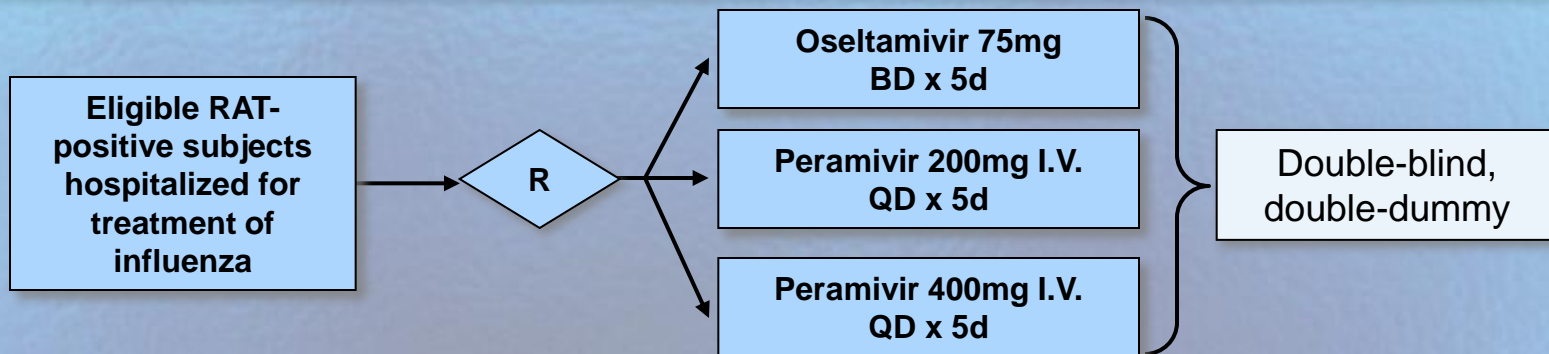
Sorbello *et al.* 50th ICAAC, Boston, MA, Sept. 13, 2010, Abstract V-658.

Hernandez *et al.*, Clin Infect Dis 2011; 52 : 695-706

IV Peramivir eIND Survival



BCX1812-201: *Methods & Endpoints*

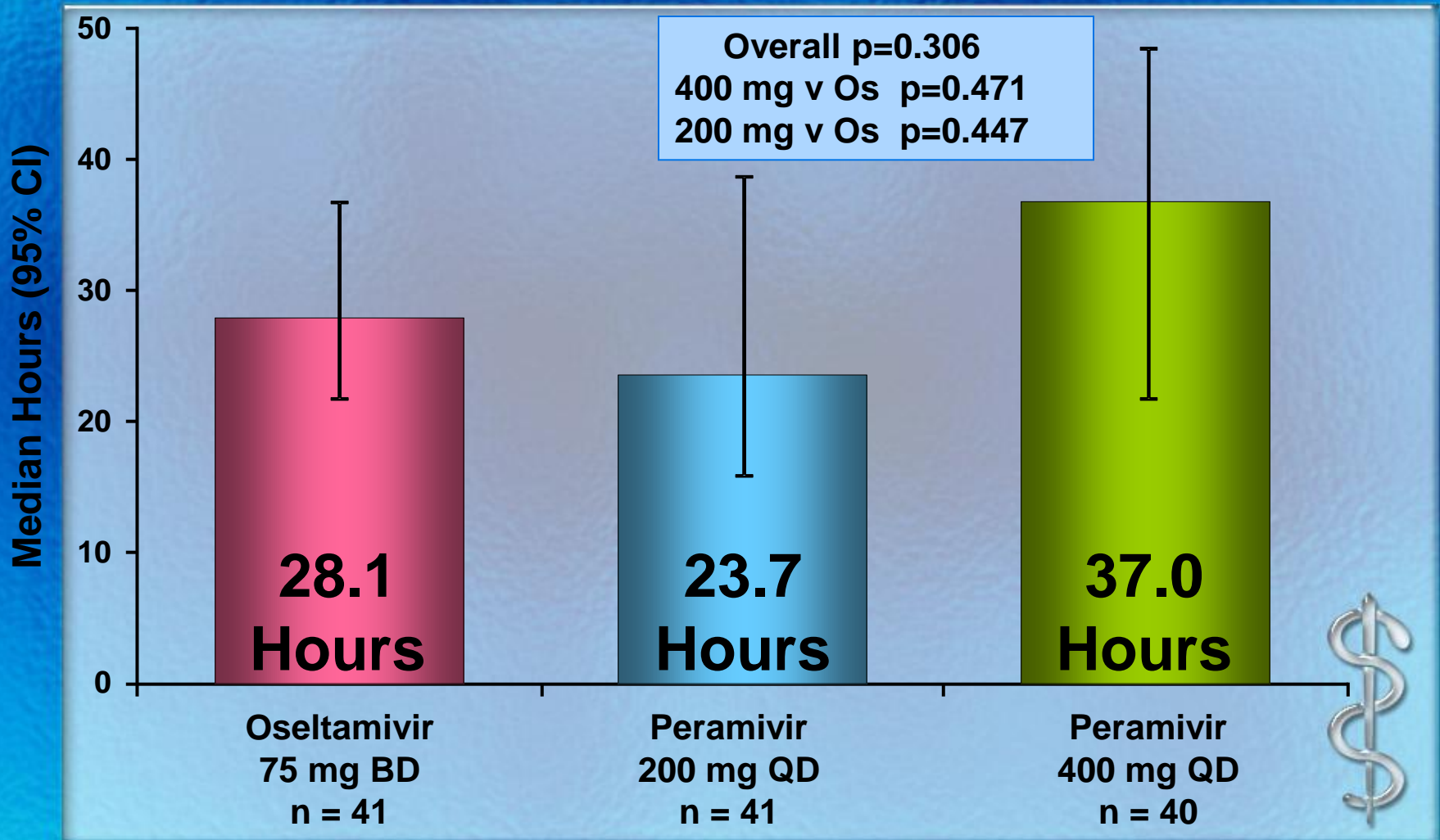


- Primary Endpoint - Time to Clinical Stability¹
 - 4 of the 5 clinical signs must meet normalization criteria for ≥ 24 hr
 - Temperature
 - Respiratory Rate
 - Systolic Blood Pressure
 - Oxygen Saturation
 - Heart Rate
 - Normalization of temperature and oxygen saturation mandatory
- Virologic Endpoint - Change in viral titer (\log_{10} TCID₅₀/mL)
- Secondary Clinical Endpoints
 - Time to return to usual activity
 - Change in flu symptom score
 - Incidence of flu complications
 - Incidence of relapse of influenza
 - Time to hospital discharge
 - Mortality



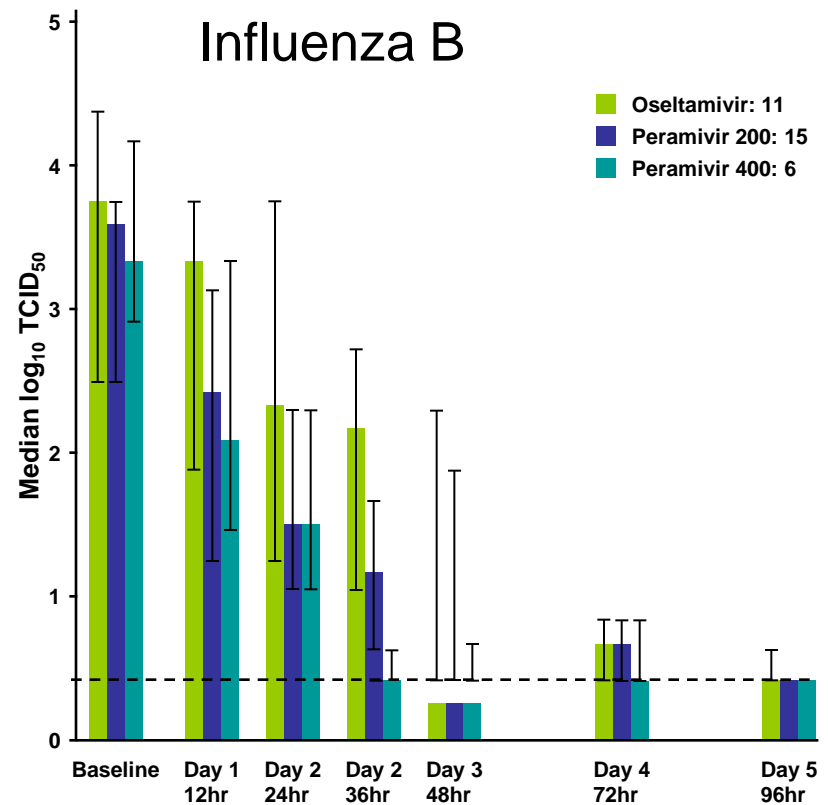
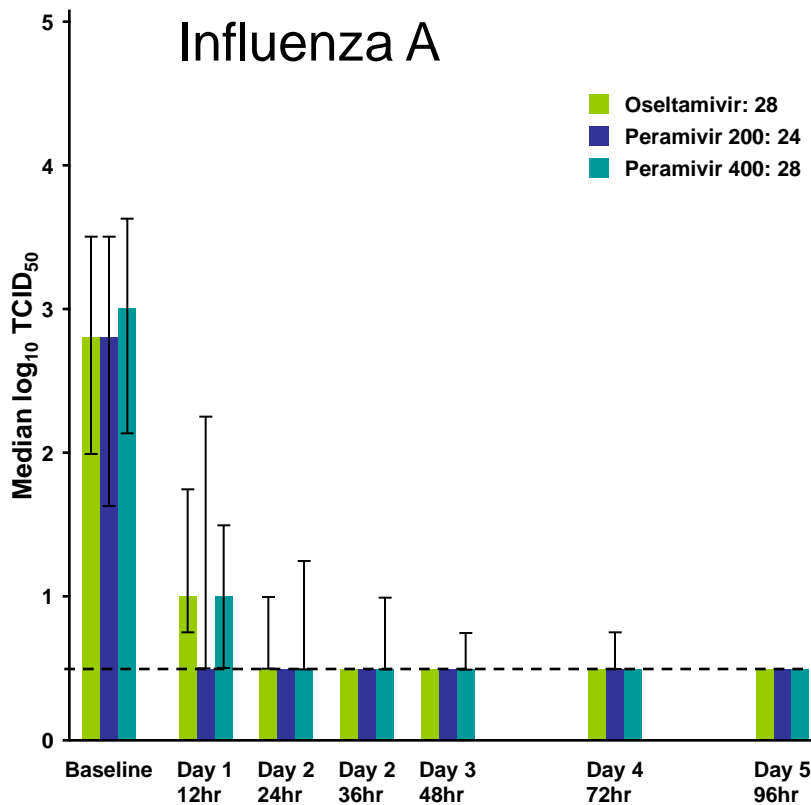
¹Adapted from: Halm *et al.* **JAMA.** 1998; 279: 1452-7.

BCX1812-201: *Time to Clinical Stability*

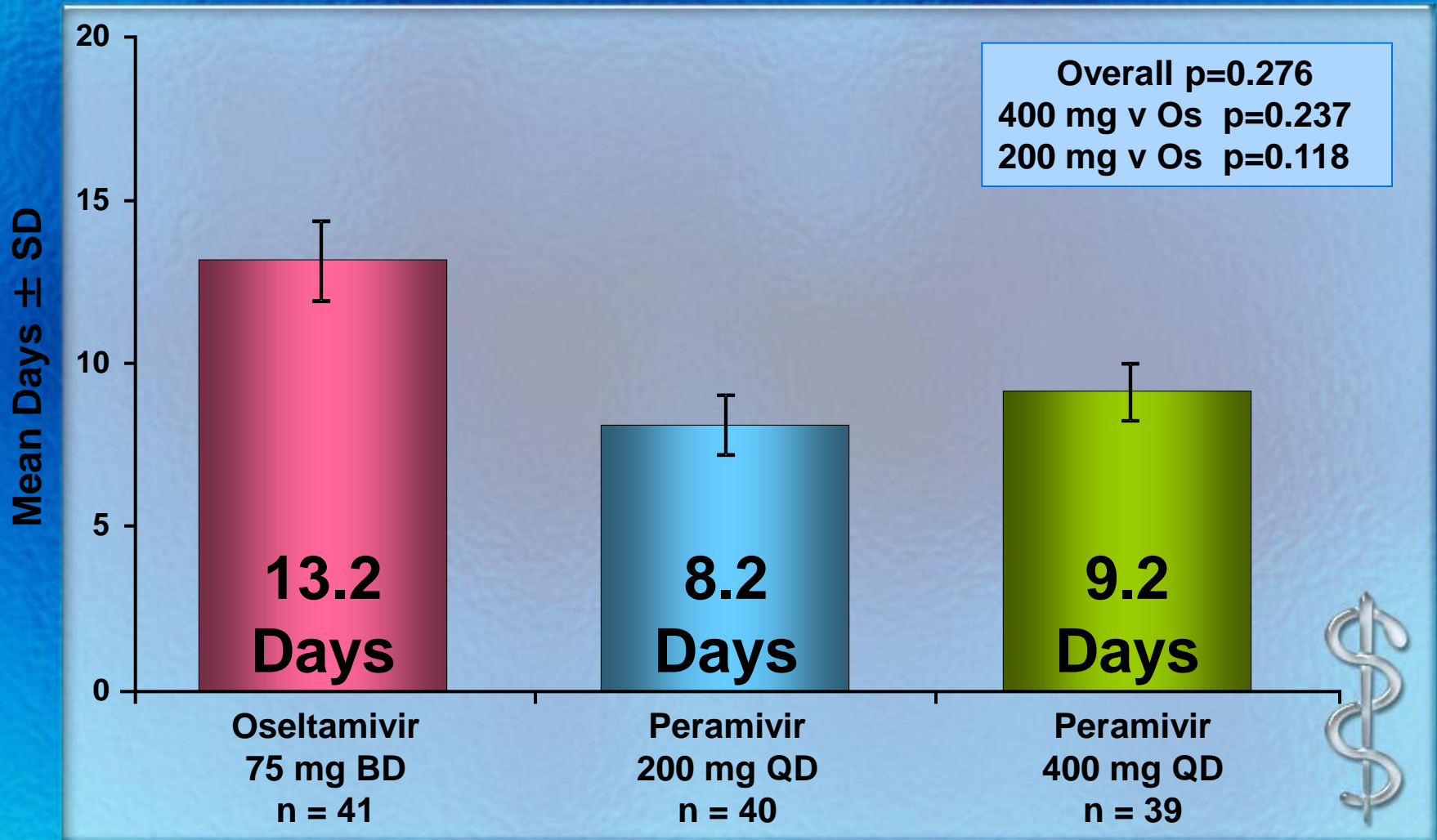


BCX1812-201: *Virologic Outcomes*

Median Viral Titers in \log_{10} TCID₅₀ by Influenza Type



BCX1812-201: *Time to Resumption of Usual Activities*



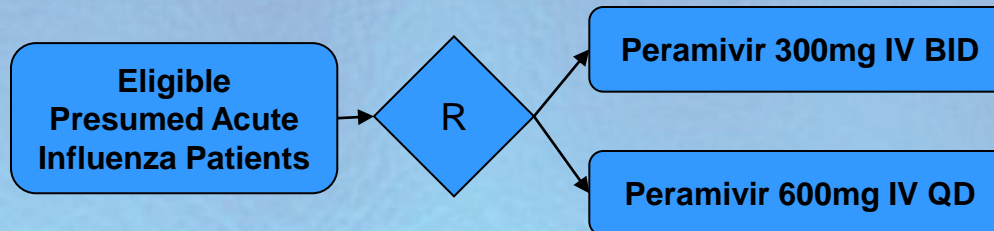
IV Peramivir ROW Phase 3 Program: *Overview*

Parameter	Study 301	Study 303
Dose Groups	PVR 600mg QD x 5 days + Std of Care vs. PBO + Std of Care	PVR 300mg BID x 5 days: PVR 600mg QD x 5 days
Allocation ratio	2:1	1:1
Power	90%	N/A
Endpoint	Time to Clinical Resolution	Reduction in viral titer
N Total	Sufficient to confirm 160 in primary analysis population (Goal Enrollment: up to 600)	234
Patient Population	Requires hospitalization and presence of one or more risk factors	Hospitalized patients, Broad inclusion
Sites	265	140
Location	U.S./ Canada/ Eastern & Western Europe/ Baltic/Latin America//S. Africa	U.S. / Canada / Mexico / Australia/NZ

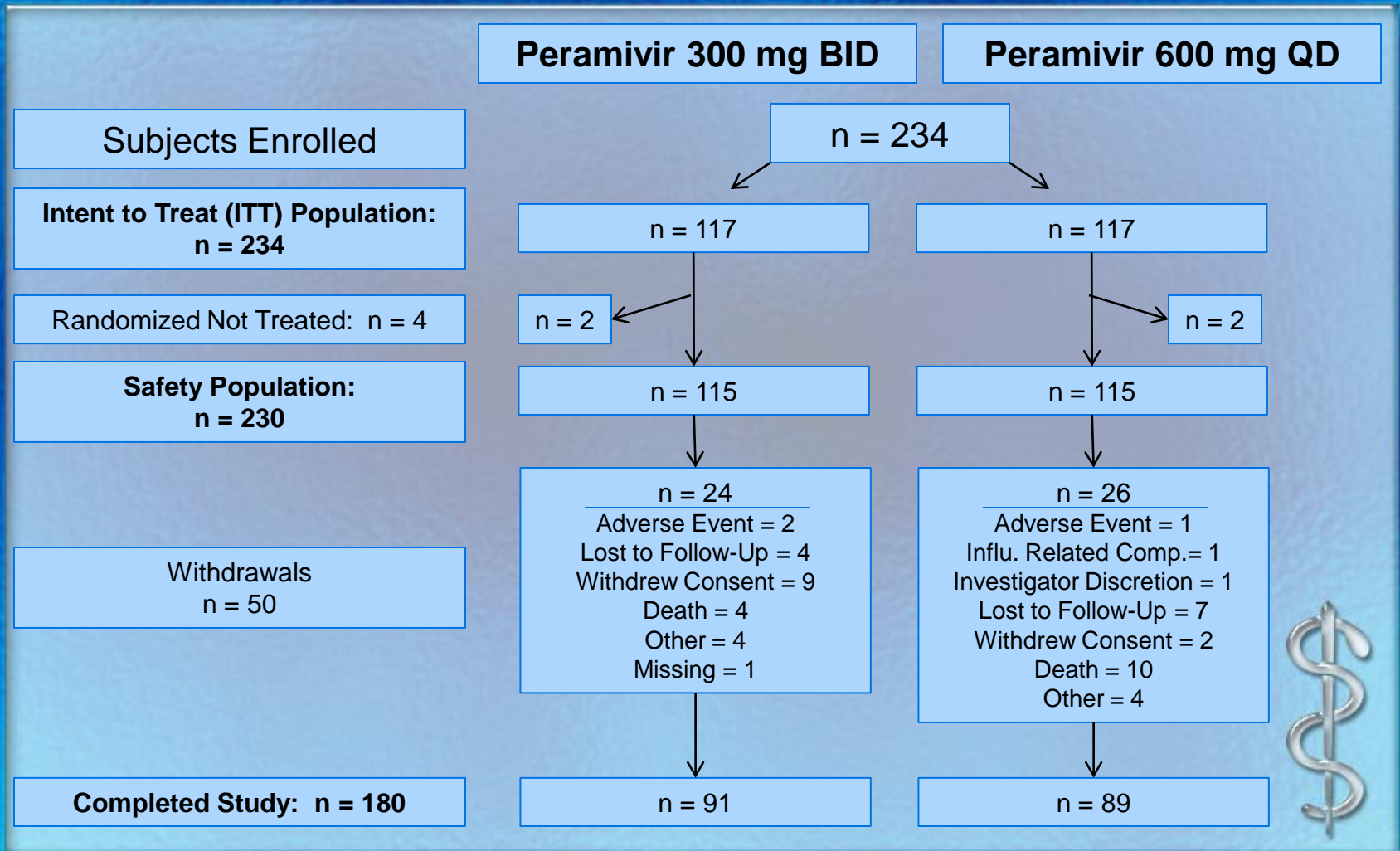


BCX1812-303: *Study Design*

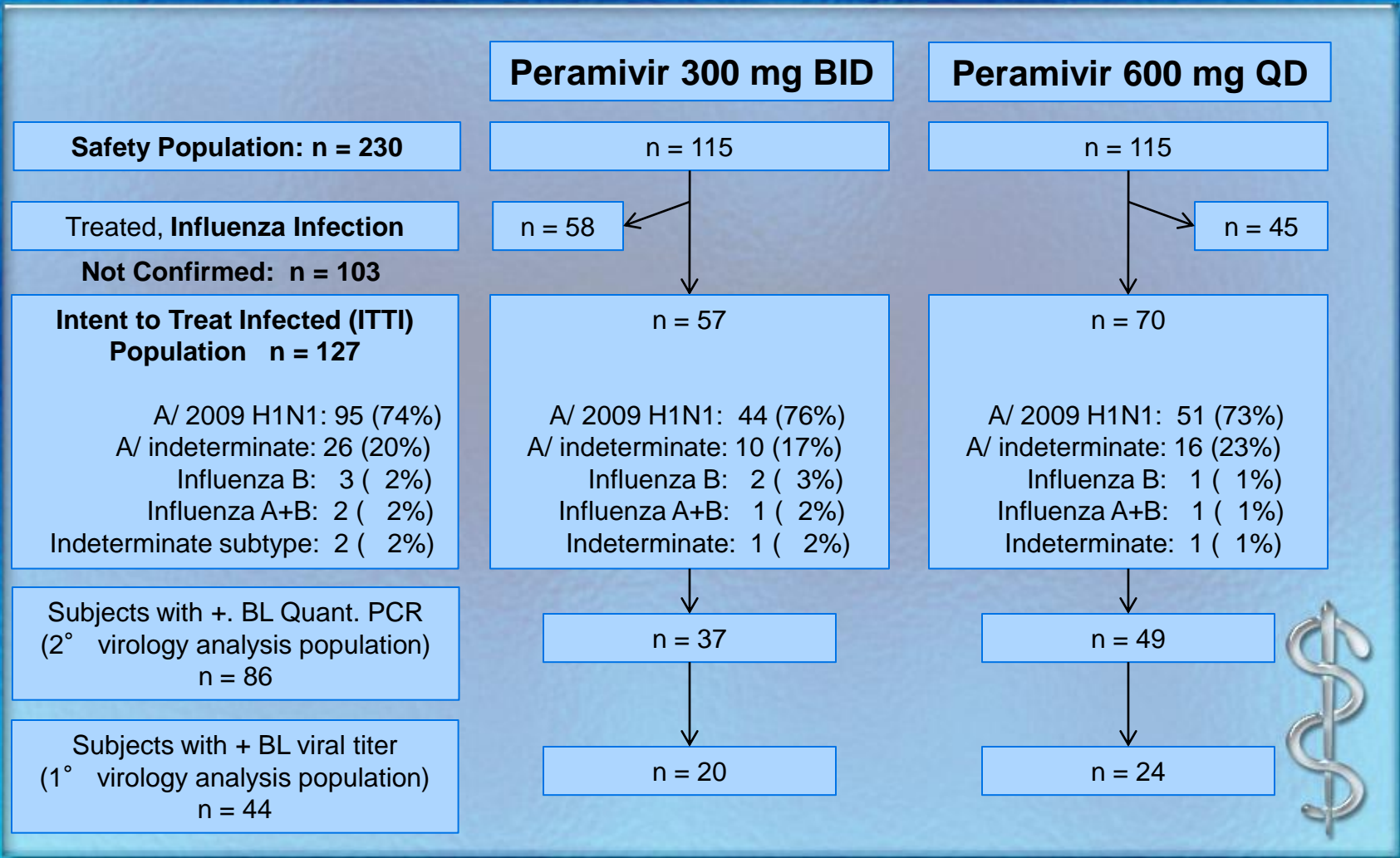
- Open-label, randomized study of antiviral activity, safety and tolerability
- Broad inclusion criteria
 - Presence of clinical signs and/or symptoms consistent with an acute illness compatible with influenza infection
 - Confirmation of influenza A or B infection in the local community
 - Severity of illness requiring or anticipated to require in- hospital care
- Exclusion criteria: no restriction on prior use of NAIs
- Sample size ~300 subjects
 - Powered to detect a 0.24 using \log_{10} TCID₅₀ time-weighted change from baseline to 48-hours in influenza viral titer
- Primary Endpoint
 - Change (reduction) in influenza virus titer measured by \log_{10} tissue culture infective dose (TCID₅₀)
- Stratified enrollment according to duration of illness: ≤ 48 vs. > 48 h



BCX1812-303: *Study Population*



BCX1812-303: *Virology Population*

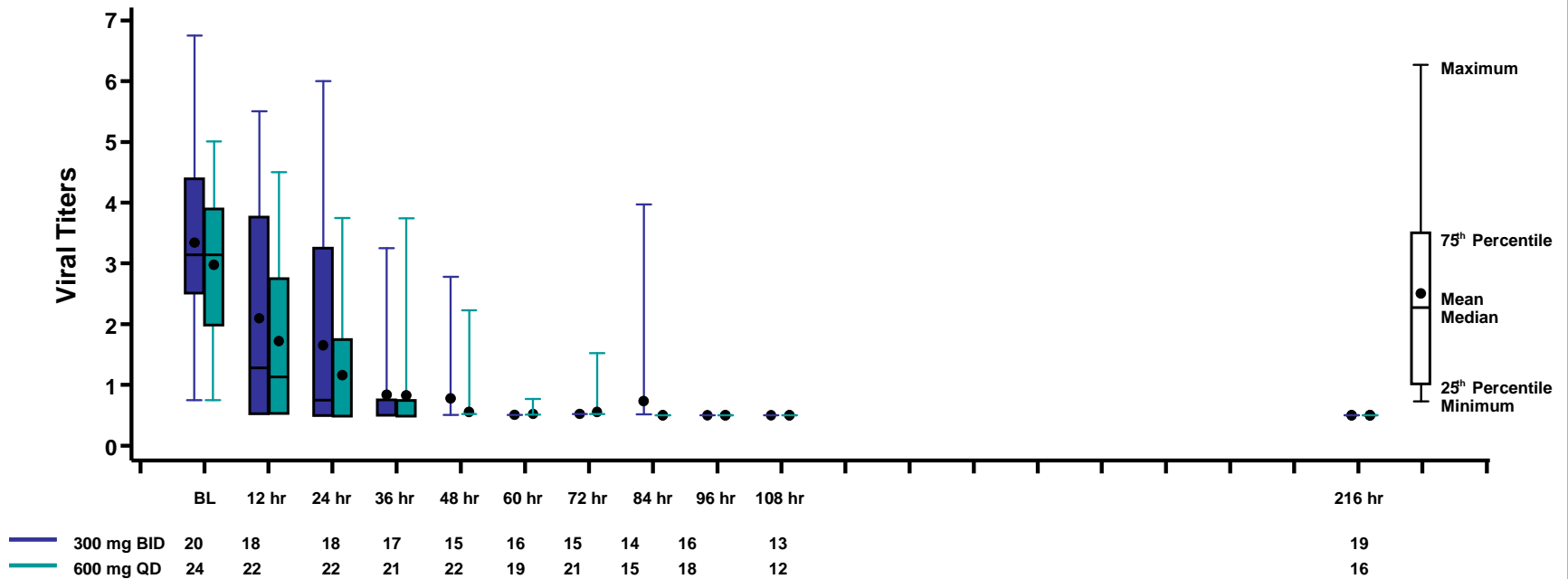


BCX1812-303: ITTI Demographics

Parameter	Peramivir 300 mg BID n = 57	Peramivir 600mg QD n = 70
Age, median (min, max)	45.4 (14.3, 92.5)	46.3 (18.9, 88.1)
Adolescent (12-17 years old)	1	0
Gender: female	36 (63%)	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	20 (35%)	27 (39%)
Vaccination status: Not vaccinated this year	35 (61%)	50 (71%)
Duration of illness:	≤48 hr	12 (17%)
	> 48 hr	58 (83%)
# of subjects requiring supplemental O ₂ at BL	35 (61%)	52 (74%)
# of subjects with ICU admission at baseline	9 (16%)	15 (21%)
APACHE II score, median (min, max) (for first ICU admission)	n = 8 12 (4, 28)	n = 12 16 (9, 28)

Primary Efficacy Analysis: *Viral Titer*

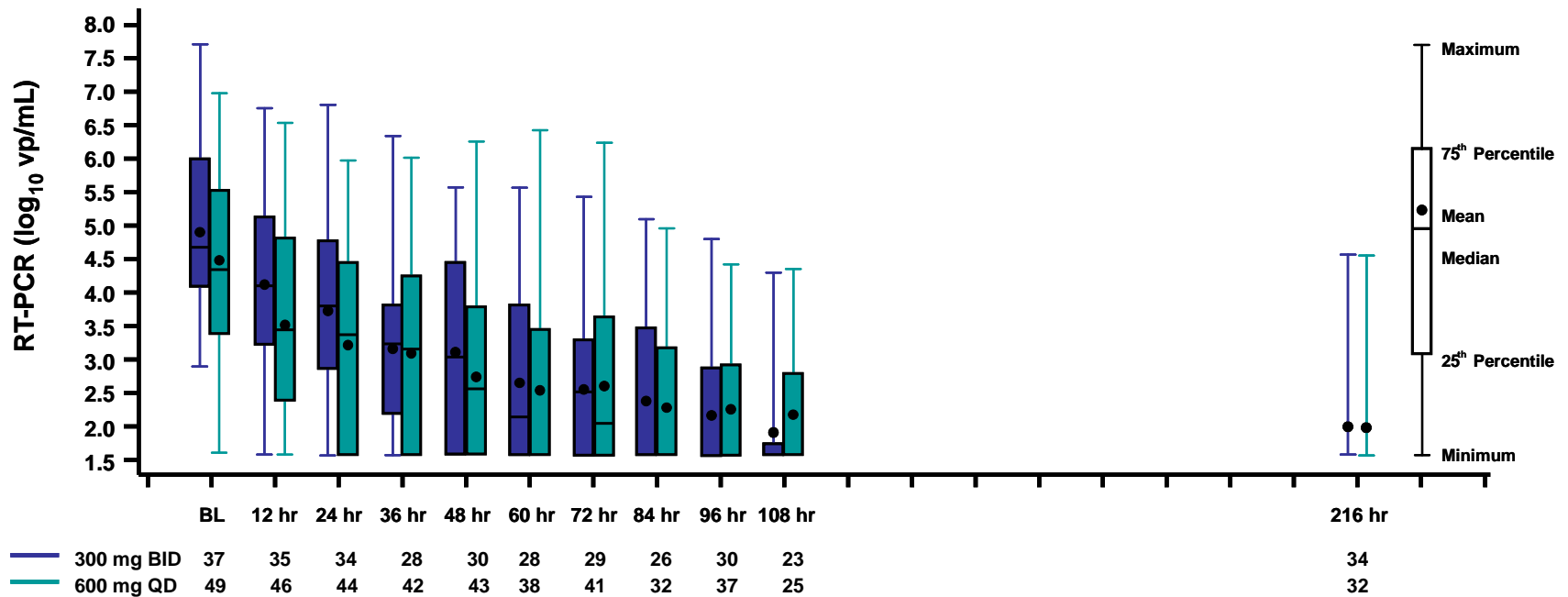
TW Change: BL to 48 hrs	Peramivir 300mg BID	Peramivir 600mg QD
N	20	24
Median (95% CI)	-1.66 (-2.32,-0.61)	-1.47 (-1.89, -0.75)
Min, Max	-3.55, -0.09	-3.37, -0.20



Note: Negative viral titer by culture is a \log_{10} TCID₅₀/mL = 0.5

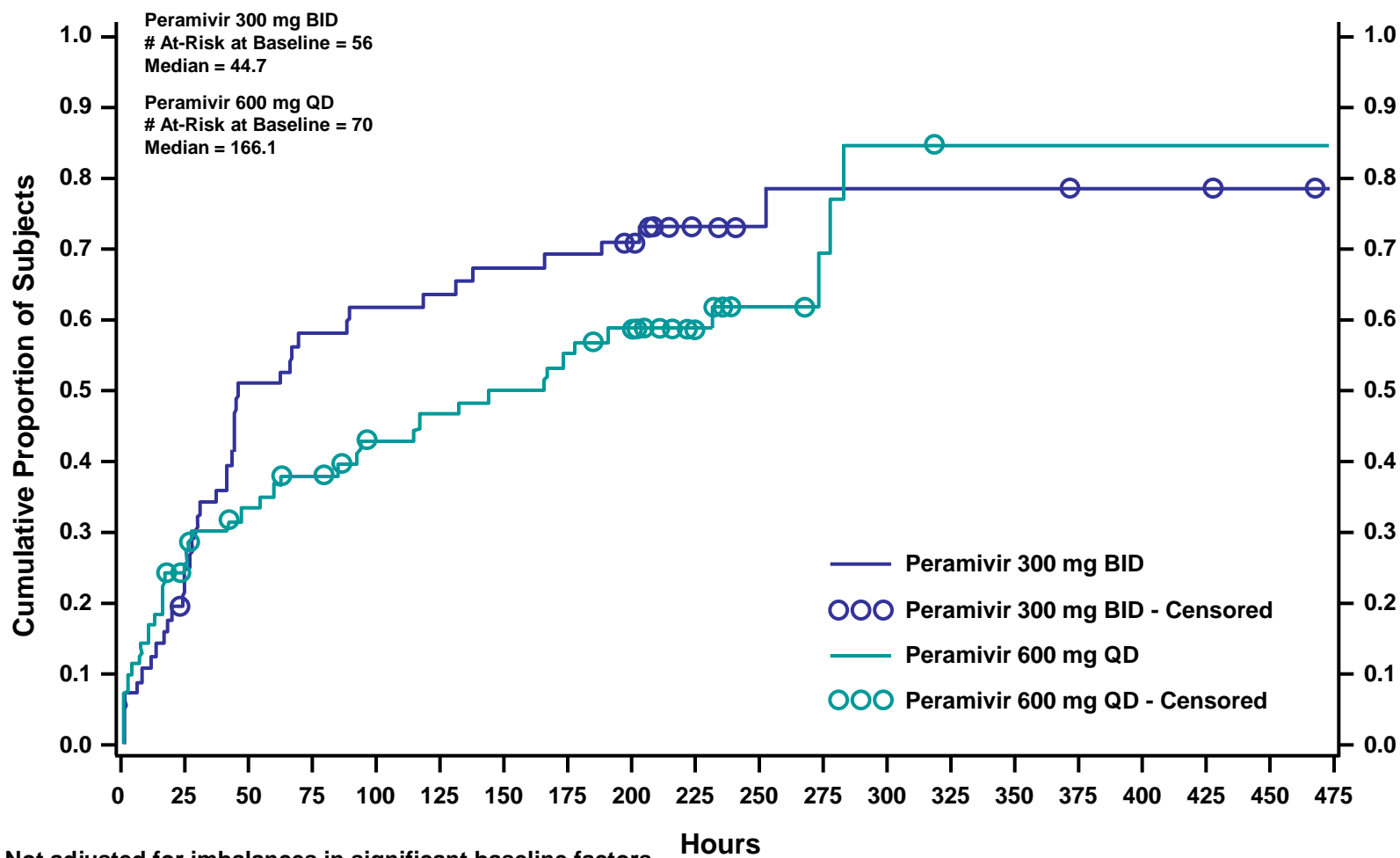
Secondary Virology Analysis: *PCR Titers*

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.

BCX1812-303: Kaplan-Meier of Time to Clinical Resolution (ITTI)



Not adjusted for imbalances in significant baseline factors

BCX1812-303: *Time to Clinical Resolution*

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)
<p>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.</p>		

BCX1812-303: *Other Clinical Endpoints*

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%

BCX1812-303: *Safety – AE Summary*

- The overall adverse event rate was 76% in safety pop.
- The most common System Organ classes with AEs were:

– GI	37%	– Respiratory	27%
– Metabolism	26%	– Infections	25%
– General disorders	20%		

- The most common individual AEs reported were:

– Constipation	13%	– Diarrhea	13%
– Hypokalemia	10%	– Hypotension	8%
– Anemia	8%	– Nausea	8%
– Peripheral edema	8%		



BCX1812-303: *Safety – SAE Summary*

- Overall rate of SAEs was 20%.
- The most common System Organ Classes with SAEs were:
 - Respiratory 9%
 - Renal 3%
 - Vascular disorders 2%
 - Infections 8%
 - Cardiac 2%
- The most common individual SAEs reported were:
 - Respiratory failure 3%
 - Septic Shock 2%
 - All the rest were $\leq 1\%$ and usually single reports
 - ARDS 2%
 - Acute renal failure 2%
- Looking at some composites of similar medical concepts:
 - Pneumonia* was 3% although each individual event was $\leq 1\%$
 - Respiratory insufficiency^o was 4%
 - Renal failure remained 2%



*Reported as pneumonia, bacterial pneumonia, staphylococcal pneumonia, lower respiratory tract infection, and necrotizing pneumonia); ^o Reported as respiratory failure, acute respiratory failure, respiratory distress

BCX1812-303: 28-day Mortality Analysis

Subgroup	300 mg BID	600mg QD	P Value between regimens*
Supplemental oxygen at study entry (n=158)	7/75 (9%)	12/83 (13%)	0.455
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%)	0.379
No ICU at study entry (n=191)	7/97 (7%)	7/94 (7%)	

Effect of requirement 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 Cochran-Mantel-Haenszel General Association statistic controlling for condition (ICU admission or supplemental O₂ use). ** P-value is based on a χ^2 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 differences were observed in the primary or secondary virology endpoints studied
- 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 population appears representative of the hospitalized patient population in the US during the 2009-2010 pandemic
- 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 very similar to the rate reported by FDA in their peramivir EUA Medwatch safety analyses presented at ICAAC.
- 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



Questions?

Michael G. Ison, MD MS
312-695-5085
mgison@northwestern.edu

