Antiviral Susceptibility of Influenza Viruses after Therapy (Rx) with Peramivir (PVR) Vs. Placebo (PBO) or Oseltamivir (OSE) in Influenza Subjects in Phase 2 and 3 Trials. Jaime E. Hernandez[1], Michael Ison[2], George Atiee[3], Shigeru Kohno[4], James Alexander[1], Jenna Elder[5], Phil Collis[1]. [1]BioCryst Pharma., Durham, NC, [2]NW Univ. School of Med., Chicago, IL, [3]Health Care Disc., San Antonio, TX, [4]Nagasaki Univ., Japan, [5]PharPoint Res., Wilmington, NC, USA.

Background: Neuraminidase inhibitor (NAI) resistance potentially limits influenza Rx. We assessed Δ in NAI sensitivity with virology from 3 phase 2 studies comparing PVR to PBO or OSE in outpatient (OP) or hospitalized (IP) subjects, & 1 uncontrolled phase 3 study in IP subjects. **Methods:** NP swabs collected virus. RT PCR, culture or paired serology confirmed influenza A subtype and B infection; pyrosequencing checked H275Y status in H1N1 in 1 study, & $TCID_{50}$ quantified virus (BL to days 5 or 10). BL & post-Rx MUNANA phenotypes were done. Two genotyping (GT) subsets were defined: paired isolates with NAI IC_{50}s > BL mean + 2 SD (SD subset), & subjects culture + at day 5 or 9 (delayed clearance). **Results:** 1007 subjects were treated (9 countries, 6 seasons, 2006-2010). 214 got PBO, 113 single dose (sd) IM PVR 150mg, 115 sdIM PVR 300mg, 99 sdIV PVR 300mg, 99 sdIV PVR 600mg, 46 5 day (5d) PO OSE, 45 5dIV PVR 200mg QD, 46 5dIV PVR 400mg QD, 114 5-10dIV PVR 300mg BID, & 116 5-10dIV PVR 600mg QD. At BL 316 subjects had seasonal A/H1N1WT (A/sH1N1), 298 A/H3N2, 108 B & 44 A/Ind.; 3 subjects (IP study) had A/sH1N1H275Y, & 94 2009A/H1N1. Table shows BL IC_{50} by type & NAI & Δ in IC_{50} (BL to last + culture) in culture + subjects. In the sd studies, paired GTs found 7 subjects (1.6%) with post-BL H275Y strains (SD subset n=31 [7.7%]; delayed clearance n=19 [4.7%]). In the 5-10d studies, paired GTs (SD n=13; delayed clearance n=18) found only 1 subject (0.5%) with post-BL H275Y (2009 A/H1N1, prior OSE Rx).

Virus	Subjects	BL IC_{50} nM Mdn (Min, Max)		
		PVR	OSE	ZAN
A/sH1N1 WT	n = 242	1.01 (0.01, 9.43)	1.84 (0.03, 78.69)	2.76 (0.02, 42.33)
A/sH3N2	n = 264	0.31 (0.01, 6.97)	0.81 (0.03, 38.66)	0.76 (0.01, 7.80)
A/2009H1N1	n= 47	0.09 (0.01, 0.14)	0.41 (0.18, 1.26)	0.22 (0.02, 0.57)
B	n=91	2.83 (0.04, 22.13)	18.65 (0.05, 102.62)	4.19 (0.03, 32.11)
Virus	**Subjects**	**Mdn (Min, Max) IC_{50} Fold Δ from BL**		
		PVR	**OSE**	**ZAN**
A/sH1N1 WT	n= 179	1.00 (0.04, 69.50)	1.00 (0.04, 36.92)	0.97 (0.08, 40.00)
A/sH3N2	n= 210	1.09 (0.04, 177.50)	1.03 (0.03, 36.39)	1.10 (0.03, 141.00)
A/2009H1N1	n= 33	1.00 (0.58, 3102.00)	0.98 (0.39, 882.50)	1.00 (0.28, 1.69)
B	n=86	0.98 (0.02, 15.25)	0.92 (0.03, 22.73)	0.91 (0.11, 8.66)

Conclusions: BL IC_{50}s for WT influenza A & B were: PVR < ZAN < OSE. In general, little Δ in IC_{50}s post-BL was seen. Few subjects shed virus at day 5-10; few paired isolates had post-BL > 2 SD Δ in IC_{50}. GTs could not be done in all specimens, but only 8 viruses (SD subset, approx. 1%) for which the GT was determined had a post-BL known resistance mutation (all H275Y).