Virologic Analysis of Influenza Viruses after Therapy with a Single Intramuscular (IM) Dose of the Neuraminidase Inhibitor (NAI) Peramivir (PVR) Versus Placebo (PBO) in Patients with Influenza in the Outpatient (OP) Setting.

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Background: Concerns about NAI resistance have been raised. We assessed resistance development using virology from a phase 2 study comparing IM PVR to PBO in OP subjects.

Methods: Virus was collected from NP swabs. RT PCR, culture or serology confirmed influenza A subtype and B infection, and $TCID_{50}$ quantified virus from BL through day 9. Phenotypes using MUNANA were done at BL and post-treatment. Two genotyping (GT) subsets were defined: paired isolates with NAI IC_{50}s > BL mean + 2 SD, and subjects culture positive at day 9.

Results: 313 subjects enrolled in 7 countries in 2 seasons (2006/2007), (81 A/H1N1, 161 A/H3N2, 65 B and 6 A ind.) and received PBO (107), single dose IM PVR 150mg (104) or IM PVR 300mg (102). $TCID_{50}$/mL (BL to 48 hr) was Δ by a median of -3.25 logs (PVR 150), -3.25 logs (PVR 300), & -2.75 logs (PBO, $p<0.001$). The table shows BL IC_{50} by type and NAI and Δ in IC_{50} (BL to last + culture). Paired GTs in the IC_{50} > mean + 2 SD subset (n=20 [7.5%]) found 2 subjects with emergent H275Y mutation (1 in each PVR dose); the subset with delayed viral clearance (n=18 [5.7%]) saw no emerging NA resistance.

Virus	**Subjects**	**BL IC_{50} nM Mdn (Min, Max)**		
		PVR	**OSE**	**ZAN**
A/H1N1	n = 58	0.1 (0.01, 5.5)	1.0 (0.03, 64.4)	0.6 (0.02, 42.3)
A/H3N2	n = 136	0.1 (0.01, 3.4)	0.4 (0.03, 31.7)	0.4 (0.01, 6.5)
B	n = 56	2.4 (0.04, 10.3)	15.4 (0.05, 80.5)	3.7 (0.03, 14.3)
Virus	**Group**	**Mdn (Min, Max) IC_{50} Fold Δ from BL**		
		PVR	**OSE**	**ZAN**
A/H1N1 WT, n = 64	PBO, n=27	0.6 (0.04, 14.0)	1.0 (0.2, 7.9)	1.0 (0.1, 14.0)
	PVR 150, n=18	2.0 (0.2, 69.5)	1.1 (0.1, 28.8)	0.7 (0.1, 14.6)
	PVR 300, n=19	1.1 (0.04, 29.3)	1.4 (0.3, 36.9)	1.1 (0.5, 23.5)
A/H3N2, n = 111	PBO, n=44	1.1 (0.2, 18.0)	1.0 (0.2, 23.6)	1.2 (0.1, 25. 4)
	PVR 150, n=37	1.2 (0.1, 53.0)	1.0 (0.1, 6.2)	1.3 (0.2, 6.0)

	PVR 300, n=30	1.4 (0.3, 37.7)	1.2 (0.3, 36.4)	1.4 (0.1, 36.1)
B, n= 51	PBO, n=18	1.1 (0.5, 3.0)	1.1 (0.2, 2.5)	1.0 (0.3, 2.4)
	PVR 150, n=14	1.0 (0.2, 2.1)	1.0 (0.2, 1.2)	1.1 (0.7, 2.7)
	PVR 300, n=19	0.9 (0.03, 1.9)	1.0 (0.1, 1.4)	1.0 (0.4, 3.1)

Conclusions: BL IC_{50}s for influenza A & B were: PVR < ZAN < OSE. PVR significantly decreased influenza titers. Little Δ in IC_{50}s post BL was seen. Few subjects shed virus at day 9; few paired isolates had post-BL > 2 SD Δ in IC_{50}. GTs could not be obtained in all specimens, but only 2 viruses (IC_{50} > mean + 2 SD subset) for which the GT was determined had an emergent known resistance mutation.