

No Pharmacokinetic (PK) Interactions Observed Between Intravenous (IV) Peramivir and Oral (PO) Oseltamivir or Rimantadine in Humans

A1-2001

K Lasseter¹, G Atiee², S Baughman³, A McCullough⁴, P Collis⁴, A Hollister⁴ and J Hernandez⁴

¹Clinical Pharmacology of Miami, Miami, FL, USA; ²ICON Development Solutions, San Antonio, TX, USA; ³ProPharma Services, Ventura, CA, USA; ⁴BioCryst Pharmaceuticals, Durham NC, USA

ABSTRACT

BACKGROUND: IV peramivir (PVR), a neuraminidase inhibitor approved for treatment of influenza in Japan, is in Phase 3 trials in hospitalized influenza patients. It is possible peramivir may be used with other influenza antivirals. Two studies were conducted to assess the potential for a PK interaction with oseltamivir (OVR) or rimantadine (RIM).
METHODS: 21 healthy subjects were enrolled in each randomized, open-label, 3-period, 3-sequence crossover study to evaluate a single IV dose of peramivir (600 mg) and a single PO dose of oseltamivir (75 mg) or rimantadine (100 mg). All subjects received each agent alone and both agents together. The potential for a PK interaction was assessed using the 90% CI for the geometric mean ratio of peramivir C_{max} and AUC₀₋₂₄ and AUC₀₋₄₈ with/without co-administration of oseltamivir or rimantadine.
RESULTS: Assessment of the 90% CI for the geometric mean ratio of the peramivir and oseltamivir/rimantadine PK parameters showed no effect of oseltamivir or rimantadine on the PK of peramivir, and no effect of peramivir on the PK of oseltamivir or rimantadine (Table). The 90% CIs of all ratios were within the pre-specified 80 to 125% interval.

Comparisons	C _{max} (CI)	AUC ₀₋₂₄ (CI)	AUC ₀₋₄₈ (CI)
PVR plus OVR vs. PVR alone	103.8% (99.9%, 107.8%)	101.3% (98.8%, 103.8%)	101.3% (98.8%, 103.9%)
PVR plus OVR vs. OVR alone	101.3% (96.7%, 106.1%)	100.0% (97.4%, 102.6%)	100.9% (98.8%, 103.1%)
PVR plus RIM vs PVR alone	100.8% (96.3%, 105.4%)	96.7% (93.3%, 99.8%)	96.8% (93.9%, 99.7%)
PVR plus RIM vs RIM alone	105.7% (100.0%, 111.7%)	103.3% (100.2%, 106.6%)	106.0% (101.2%, 111.0%)

CONCLUSIONS: No evidence of a PK interaction was found when IV peramivir 600 mg was administered with PO oseltamivir 75 mg or PO rimantadine 100 mg. These data confirm that the concomitant administration of peramivir with either of these two antivirals in the treatment of influenza would not adversely affect the PK profile of either drug.

INTRODUCTION

- Peramivir is an intravenous neuraminidase inhibitor (NAI) in Phase 3 trials in the US and approved in Japan for treatment of influenza
- During the 2009 influenza A (H1N1) pandemic, peramivir was available by FDA eIND and EUA for patients hospitalized with severe influenza
- Most patients treated with peramivir by eIND had previous and/or concurrent treatment with other antivirals, including oseltamivir or rimantadine¹
- Osetamivir, a prodrug of oseltamivir carboxylate, is an approved NAI also used to treat influenza A and B, including the influenza A 2009 H1N1 pandemic strain
- Rimantadine, another marketed antiviral, treats influenza A by interfering with the replication cycle
- Peramivir is excreted by renal clearance unchanged in the urine, while oseltamivir and rimantadine are extensively metabolized by the liver; protein binding of all 3 drugs is low
- In vitro and in vivo animal studies did not show any interaction between oseltamivir and peramivir, or between rimantadine and peramivir^{2,3}
- These 2 studies were conducted to evaluate the effects of single dose oral oseltamivir or rimantadine on PK and safety of single dose IV peramivir and the effects of peramivir on oseltamivir or rimantadine

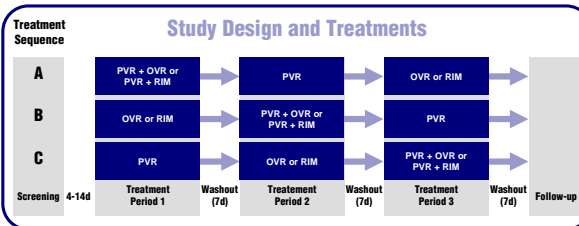
METHODS

Study Subjects

- Healthy male and female volunteers 18-60 years of age
- Non-smoking, non-obese, and not pregnant or breast feeding
- Good general health, including normal ECGs and vital signs
- Creatinine clearance ≥ 80 mL/min
- Using acceptable birth control methods, abstinent, or not of childbearing potential
- No presence or history of significant disease, syncope, arrhythmias, alcoholism, or drug abuse
- No use of prescription drugs for acute illness within 7 days or OTC drug within 3 days
- No chronic illness that requires ongoing prescription drugs

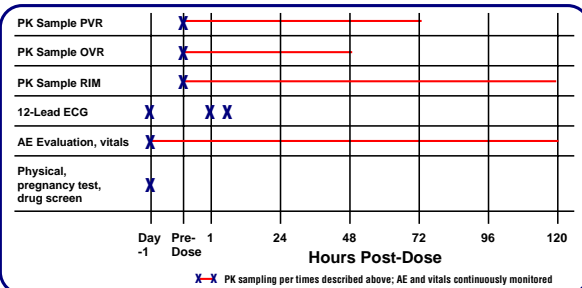
Study Design and Treatments

- Randomized, open-label, 3-way crossover studies with 7-day washout periods between treatments
- Primary endpoint measure was pharmacokinetic parameters for each drug and assessment of PK interactions when drugs co-administered
- Study 1
 - Peramivir 600 mg IV (adult recommended dose) (PVR)
 - Osetamivir 75 mg PO (OVR)
 - Peramivir + osetamivir
- Study 2
 - Peramivir
 - Rimantadine 100 mg PO (RIM)
 - Peramivir + rimantadine
- Concomitant medications were avoided during the study, except low-dose aspirin, acetaminophen, oral contraceptives, or HRT
- IV peramivir 10 mg/mL infused over 15 minutes
- In subjects receiving peramivir + osetamivir or peramivir + rimantadine, oral drug was taken at start of infusion



Study Assessments

- At screening, medical history, physical exam, clinical safety labs, drug screen, pregnancy test, serology for HBV, HCV, and HIV, and 12-lead ECGs conducted
- Admission to clinical unit for each treatment period for assessments shown below
- Blood sampling for peramivir PK analysis 5 min pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72 hr post-dose
- Blood sampling for oseltamivir PK analysis 5 min pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hr post-dose
- Blood sampling for rimantadine PK analysis 5 min pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96, and 120 hr post-dose
- Discharge from clinical unit after 24-hr sample and return for 48-hr, 72-hr, 96-hr, and 120-hr samples, as applicable



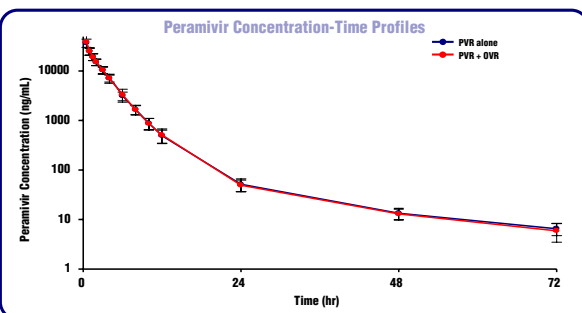
- At follow up 7 days after Treatment Period 3 or upon early termination, vital signs, AE assessments, physical exam, clinical lab tests, and a pregnancy test conducted

RESULTS

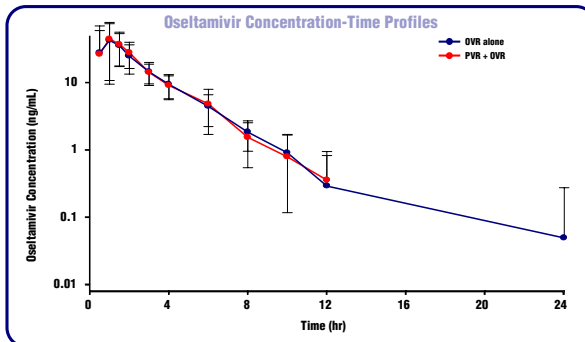
Study Subjects

- Study 1 (peramivir/oseltamivir)
 - 21 subjects enrolled and randomized to the 3 treatment sequences (7 per sequence)
 - 52% of the subjects female
 - Treatment sequences similar in demographic and clinical characteristics
- Study 2 (peramivir/rimantadine)
 - 21 subjects enrolled and randomized to the 3 treatment sequences (7 per sequence)
 - 57% of the subjects female
 - Treatment sequences similar in demographic and clinical characteristics
 - 20 subjects completed, 1 subject discontinued for an AE (viral gastroenteritis) from Treatment Sequence B prior to receiving peramivir alone

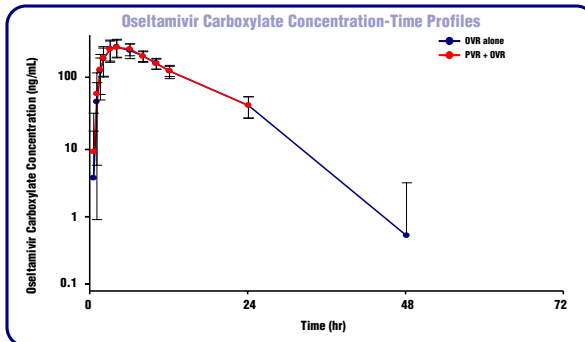
Pharmacokinetic Profiles in Study 1 (Peramivir/Osetamivir)



- Mean (+/- SD) concentration-time profiles (semi-logarithmic) for peramivir after peramivir administration with or without oseltamivir were very similar



- Mean (+/- SD) concentration-time profiles (semi-logarithmic) for osetamivir after osetamivir administration with or without peramivir were very similar



- Mean (+/- SD) concentration-time profiles (semi-logarithmic) for osetamivir carboxylate after osetamivir administration with or without peramivir were very similar

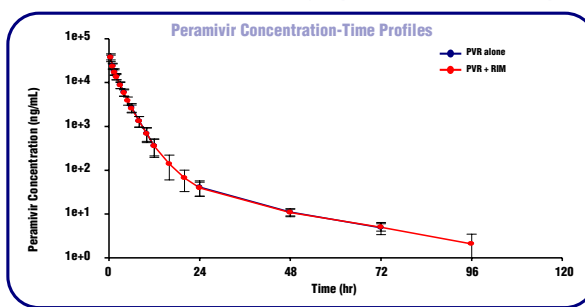
Mean (±SD) Peramivir PK Parameters Following Intravenous Injection and Osetamivir Carboxylate PK Parameters Following Oral Administration

Parameter	Peramivir		Osetamivir Carboxylate	
	PVR (N=21)	PRV + OVR (N=21)	OVR (N=21)	PVR + OVR (N=21)
C _{max} (ng/mL) ¹				
Mean (SD)	37230 (7045)	38470 (6273)	283 (76.4)	284 (60.4)
T _{max} (h)				
Mean (SD)	0.50 (0.50, 0.53)	0.50 (0.50, 0.55)	4.00 (3.00, 8.00)	4.00 (3.00, 6.00)
AUC ₀₋₂₄ (ng*hr/mL) ¹				
Mean (SD)	89230 (12950)	90380 (12580)	3260 (643)	3240 (543)
AUC _{0-inf} (ng*hr/mL) ¹				
Mean (SD)	89380 (12990)	90530 (12620)	3670 (700)	3690 (617)

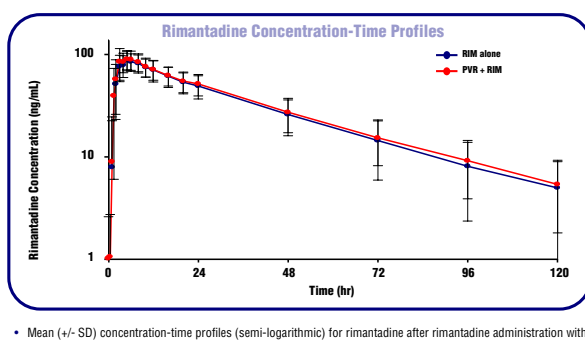
¹The least square means and confidence intervals are based on an ANOVA model of the natural log transformed parameter (using a mixed effects repeated measures ANOVA model with fixed effects for treatment, period, and sequence, and a random effect for subject nested in sequence).

- Key PK parameters for peramivir after peramivir administration with or without oseltamivir were very similar
- Key PK parameters for osetamivir carboxylate after osetamivir administration with or without peramivir were very similar

Pharmacokinetic Profiles in Study 2 (Peramivir/Rimantadine)



- Mean (+/- SD) concentration-time profiles (semi-logarithmic) for peramivir after peramivir administration with or without rimantadine were very similar



- Mean (+/- SD) concentration-time profiles (semi-logarithmic) for rimantadine after rimantadine administration with or without peramivir were very similar

Mean (±SD) Peramivir PK Parameters Following Intravenous Injection and Rimantadine PK Parameters Following Oral Administration

Parameter	Peramivir		Rimantadine	
	PVR (N=20)	PVR + RIM (N=21)	RIM (N=21)	PVR + OVR (N=21)
C _{max} (ng/mL) ¹				
Mean (SD)	37680 (7819)	37540 (4648)	92.8 (18.4)	99.0 (23.7)
T _{max} (h)				
Mean (SD)	0.50 (0)	0.50 (0)	5.5 (1.6)	4.6 (1.9)
AUC ₀₋₂₄ (ng*hr/mL) ¹				
Mean (SD)	80230 (12450)	77020 (10150)	1520 (320)	1570 (328)
AUC _{0-inf} (ng*hr/mL) ¹				
Mean (SD)	81170 (12570)	77990 (10290)	3590 (1290)	3780 (1190)

¹The least square means and confidence intervals are based on an ANOVA model of the natural log transformed parameter (using a mixed effects repeated measures ANOVA model with fixed effects for treatment, period, and sequence, and a random effect for subject nested in sequence).

- Key PK parameters for peramivir after peramivir administration with or without rimantadine were very similar
- Key PK parameters for rimantadine after rimantadine administration with or without peramivir were very similar

Comparisons	C _{max} (CI)	AUC ₀₋₂₄ (CI)	AUC ₀₋₄₈ (CI)
PVR plus OVR vs. PVR alone	103.8% (99.9%, 107.8%)	101.3% (98.8%, 103.9%)	101.3% (98.8%, 103.9%)
PVR plus OVR vs. OVR alone	101.3% (96.7%, 106.1%)	100.0% (97.4%, 102.6%)	100.9% (98.8%, 103.1%)
PVR plus RIM vs PVR alone	100.8% (96.3%, 105.4%)	96.7% (93.3%, 99.8%)	96.8% (93.9%, 99.7%)
PVR plus RIM vs RIM alone	105.7% (100.0%, 111.7%)	103.3% (100.2%, 106.6%)	106.0% (101.2%, 111.0%)

- Assessment of the 90% CI for the geometric mean ratio of the peramivir and oseltamivir/rimantadine PK parameters showed no effect of oseltamivir or rimantadine on the PK of peramivir and no effect of peramivir on the PK of oseltamivir or rimantadine
- 90% CIs of all ratios within pre-specified 80 to 125% interval

Safety

- Adverse events were reported by 29%, 29%, and 19% of subjects in the peramivir, oseltamivir, and peramivir + oseltamivir groups, respectively, in Study 1
- Adverse events were reported by 5%, 19%, and 19% of subjects in the peramivir, rimantadine, and peramivir + rimantadine groups, respectively, in Study 2
- All adverse events were mild in nature
- Most frequently reported AE was headache
- No serious AEs or deaths occurred
- In Study 2, 1 subject withdrew for an AE (viral gastroenteritis), which resolved without sequelae and was not attributed to study drug
- No clinically significant laboratory abnormalities were reported

DISCUSSION

- Results of 2 studies clearly demonstrate the lack of a PK interaction of peramivir with oseltamivir or rimantadine in healthy volunteers
- Doses of oseltamivir and rimantadine chosen for the 2 studies were relevant, marketed doses. Single doses were deemed sufficient to evaluate potential drug interactions
- Results were as expected, based on the routes of elimination, and confirm previous preclinical studies²⁻⁴
- Study medications at these doses when administered alone or together were well tolerated
- Seriously ill patients with influenza who are treated with oral oseltamivir or rimantadine can be administered IV peramivir without concern of drug interaction

CONCLUSIONS

- There was no evidence of a PK interaction when IV peramivir 600 mg was simultaneously administered with oral oseltamivir 75 mg or oral rimantadine 100 mg.
- Concomitant administration of peramivir with oseltamivir or rimantadine was generally safe and well tolerated.
- Concomitant administration of peramivir with either antiviral in the treatment of influenza would not adversely affect the PK profile of these drugs.

REFERENCES

- Hernandez J. A review of clinical experience in the treatment of severe 2009 H1N1 influenza with intravenous peramivir under an emergency investigational new drug (IND) program in the US. Presented at XII International Symposium on Respiratory Viral Infections, Taipei 2010.
- Bantia S, Parker CD, Ananth S, et al. Comparison of the anti-influenza virus activity of RIM-270021 with those of oseltamivir and zanamivir. Antimicrob Agents Chemother 2001;45:1162-1167.
- Smie DF, Hurst B, Wong M-H, et al. Efficacy of combinations of oseltamivir and peramivir in treating influenza A (H1N1) virus infections in cell culture and in mice. Antiviral Res 2010;86:447.
- Bantia S, Kallogg D, Parker C, et al. Combination of peramivir and rimantadine demonstrate synergistic interaction in influenza A mouse model. Antiviral Res 2010; 86:29

ACKNOWLEDGMENTS

The authors acknowledge the patients and study site personnel at ICON Development Solutions and Clinical Pharmacology of Miami, the study teams at BioCryst who participated in BCK1812-108 and 109, and HHS/BARDA for funding support