

# Intravenous (IV) Peramivir was not Associated with Repolarization Abnormalities in a Thorough QT/QTc Electrocardiographic (ECG) Study

A1-2000

L Satin<sup>1</sup>, G Haugen<sup>2</sup>, A Waugh<sup>3</sup>, P Collis<sup>3</sup>, J Hernandez<sup>3</sup>, A Hollister<sup>3</sup> on behalf of BioCryst Pharmaceuticals Protocol BCX1812-106  
<sup>1</sup>Cardiocore, Bethesda, MD, USA; <sup>2</sup>Cetero Research, Fargo, ND, USA; <sup>3</sup>BioCryst Pharmaceuticals, Durham, NC, USA

## ABSTRACT

**BACKGROUND:** IV peramivir, a neuraminidase inhibitor approved for treatment of influenza in Japan is in Phase 3 trials at daily doses of 600 mg for the treatment of hospitalized patients with influenza. We conducted a thorough QT/QTc study to evaluate the potential for any effect of IV peramivir on repolarization abnormalities.

**METHODS:** 52 healthy subjects were enrolled in a randomized, double-blind, placebo- and moxifloxacin-controlled 4-period crossover study evaluating two single IV doses of peramivir (600 mg and 1200 mg). This study design conformed to the FDA requirements for a Thorough QT Study. ECG data for QTc evaluation were extracted from Holter recorders before treatment and at specified intervals after administration of study drug. Pharmacokinetic (PK) samples were obtained up to 24 hours after treatment. Safety evaluations included adverse event (AE) assessments, changes in laboratory tests, and on-site review of standard 12-lead ECGs.

**RESULTS:** Neither dose of peramivir (600 mg or 1200 mg) showed a statistically significant increase for the primary endpoint, placebo-subtracted difference of QTcF. No values of QTcF >450 msec occurred during peramivir treatment. No differential effect on QTcF by gender was present. Correlation with PK data found that increasing plasma levels of peramivir were not associated with QTcF prolongation. Assay sensitivity was demonstrated by lower bounds of the 95% one-sided CIs for placebo-subtracted difference of QTcF for moxifloxacin treatment being > 5 msec at all of the 3 timepoints designated. AEs (mild or moderate in severity) were reported by 15/52 (29%) subjects enrolled. No serious AEs occurred.

**CONCLUSIONS:** IV peramivir administered at a therapeutic dose of 600 mg or at a supratherapeutic dose of 1200 mg was not associated with QTc prolongation or other repolarization abnormalities. Peramivir was generally safe and well-tolerated.

## INTRODUCTION

- Peramivir is an intravenous neuraminidase inhibitor in Phase 3 trials in the US and approved in Japan for treatment of influenza
- Previous nonclinical studies have found no effect on hERG channel current
- There were no effects of IV administration on QT interval or other ECG parameters in rats and no effects of intraduodenal administration on cardiac or circulatory function in dogs
- Previous Phase 1 clinical trials have found no effect on electrocardiographic QTc intervals or safety effects in elderly subjects<sup>1</sup> or safety effects in subjects with renal impairment<sup>2</sup> or hospitalized subjects with influenza<sup>3</sup>
- We conducted a thorough QT/QTc study to FDA requirements in order to evaluate the potential for IV peramivir to cause repolarization abnormalities

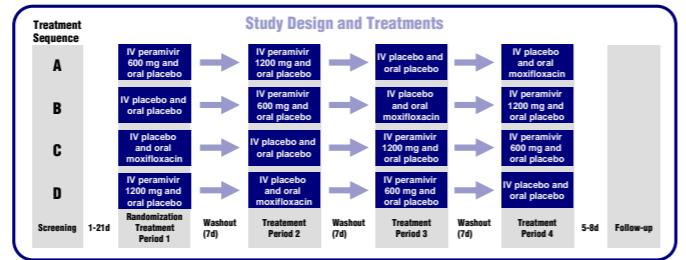
## METHODS

### Study Subjects

- Healthy volunteers 18-55 years of age
- Non-smoking, non-obese (BMI 18-30 kg/m<sup>2</sup>), and not pregnant
- Normal 12-lead ECG, no electrolyte abnormality, and no history of cardiac disease or family history of QT prolongation
- Creatinine clearance > 80 mL/min
- Using acceptable birth control methods, abstinent, or not of childbearing potential
- No history of significant disease, alcoholism, or drug abuse

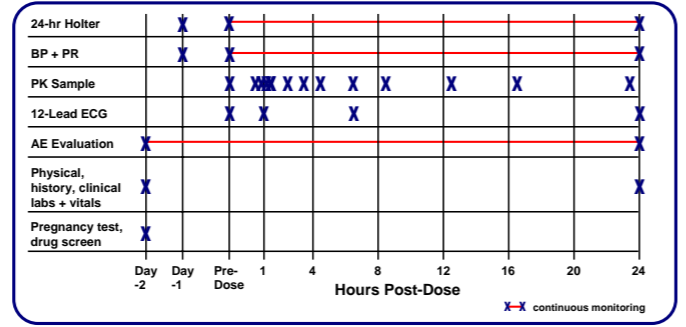
### Study Design and Treatment

- Randomized, double-blind, placebo- and moxifloxacin-controlled, 4-way crossover study with 7-day washout periods between treatment periods
- Primary endpoint measure was period-matched, baseline-adjusted, placebo-corrected change in QTcF with other corrections (QTcI, QTcB) as confirmatory assessments
- Peramivir treatment at therapeutic dose (600 mg) and supratherapeutic dose (1200 mg)
- Moxifloxacin as a positive control based on ability to increase QT interval by 12-14 msec with average T<sub>max</sub> of 2 hr
- No concomitant medications within 14 days or during study, except acetaminophen, oral contraceptives, or HRT
- IV peramivir 10 mg/mL or placebo infused over 30 minutes followed by oral over-encapsulated moxifloxacin 400 mg (Avelox<sup>®</sup>) or placebo



### 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 4-day treatment period for assessments shown below
- 24-hour Holter monitoring conducted on the day before and day of treatment with data extraction at scheduled intervals (60, 30, and 20 min pre-dose and 35, 45, 60, 75, 90, 150, 210, 270, 390, 510, 750, 990, and 1320 min on Day -1 and post-dose)
- 24-hour blood sampling for peramivir pharmacokinetic analysis 30 min pre-dose and 5 min after Holter data extraction post-dose
- Blood sampling for moxifloxacin concentrations 30 min pre-dose and up to 12.5 hr post-dose
- ECGs interpreted centrally by blinded US board-certified cardiologists



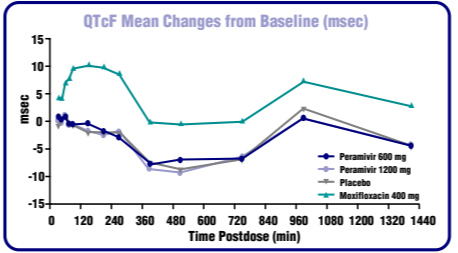
- At follow up 5-8 days after Treatment Period 4 or upon early termination, vital signs, AE assessments, 12-lead ECG, clinical lab tests, and a pregnancy test conducted

## RESULTS

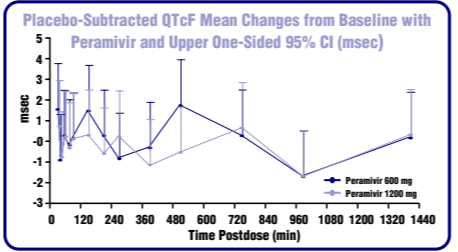
### Study Subjects

- 52 subjects enrolled and randomized to the 4 treatment sequences (13 per sequence)
- 50% of the subjects female
- Treatment sequences similar in demographic and clinical characteristics
- 3 subjects discontinued
  - 1 withdrawn for an AE (anemia) from Treatment Sequence B during Treatment Period 4
  - 1 withdrawn for positive drug screen from Treatment Sequence C during Treatment Period 3
  - 1 withdrawn for positive drug screen from Treatment Sequence D during Treatment Period 2

### QTc Effects

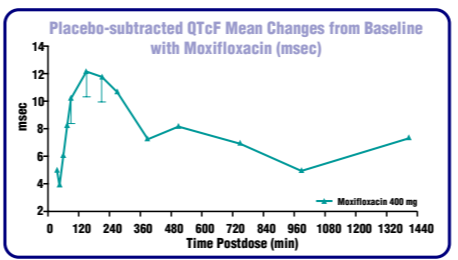


- Peramivir (both doses) and placebo treatment values were very similar at almost all timepoints
- In assessment of adequacy of QT corrections, Fridericia correction (QTcF) yielded highly efficient QTc values close to heart-rate independent
- Moxifloxacin treatment caused a distinct rise in QTcF while peramivir or placebo did not
- The moxifloxacin effect lasted until approx. 990 minutes post dose
- No QTcF intervals > 450 msec



- Time course of QTcF effects was nearly flat for both peramivir treatments
- No suggestion of a dose response
- Peramivir at these doses does not cause QTc prolongation
- Placebo-corrected change in QTcB and QTcI confirmed the result

### Assay Sensitivity

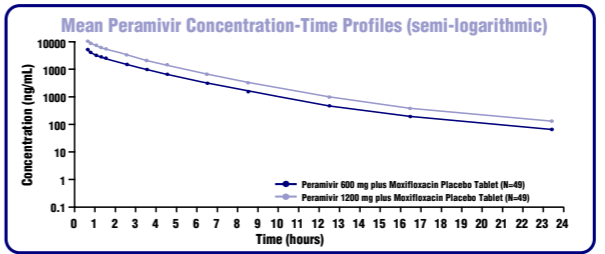


- Lower bounds of 95% one-sided CIs for placebo-subtracted difference of QTcF for moxifloxacin treatment were > 5msec at the 3 timepoints indicated
- Use of moxifloxacin as positive control demonstrated study's assay sensitivity

### Gender Analysis

- At a single timepoint (210 min) post dose, males had a significantly greater increase in QTcF than females while on 600 mg peramivir but a smaller increase while on 1200 mg (p=0.004)
- At all other measurement timepoints, differences from placebo were comparable between males and females
- Since these differences were small, at only 1 timepoint, and in opposite directions by dose, there is no indication of differential effect by gender

### Pharmacokinetic Analysis



- Consistent with previous reports (4), plasma concentrations increased quickly after IV peramivir administration
- The mean plasma concentration-time profile increased with dose

PK Parameter	Peramivir 600 mg plus Moxifloxacin Placebo Tablet (N=49)	Peramivir 1200 mg plus Moxifloxacin Placebo Tablet (N=49)
AUC <sub>0-4</sub> (ng*hr/mL)	96654.57 (± 17435.72)	199162.11 (± 34532.96)
AUC <sub>0-inf</sub> (ng*hr/mL)	96950.21 (± 17498.60)	199719.30 (± 34670.56)
C <sub>max</sub> (ng/mL)	43804.08 (± 7561.08)	93206.12 (± 14729.62)
T <sub>max</sub> * (hr)	0.67 (0.67)**	0.67 (0.67 - 0.83)

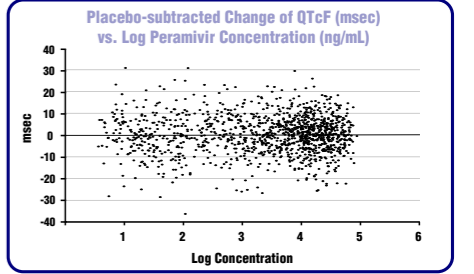
\* Median and range are reported.  
 \*\* Both minimum and maximum were 0.67

- C<sub>max</sub>, AUC<sub>0-4</sub>, and AUC<sub>0-inf</sub> increased proportionally to dose

### Safety

- Adverse events were reported by 5.8%, 7.7%, 11.5%, and 15.4% of subjects in the peramivir 600 mg, peramivir 1200 mg, placebo, and moxifloxacin groups, respectively
- All adverse events were mild or moderate
- No serious AEs or deaths occurred
- One female subject was withdrawn due to an adverse event (anemia) not attributed to study drug (heavy menstrual period)
- No clinically significant changes in laboratory results were associated with treatment

### Relationship of QTc Effects to Peramivir Concentration



- Assessed by repeated measures linear regression,
- Estimated mean differences from placebo show all upper CI limits are <1.5 msec
- No relationship between peramivir plasma concentration and increases in QTcF

## DISCUSSION

- Peramivir at either 600 mg or 1200 mg had no effect on placebo-corrected change from baseline in QTcF, the primary endpoint
- Analyses using change from baseline in QTcI and QTcB confirmed the result
- The effect of the positive control, moxifloxacin, on QTcF confirmed the assay's sensitivity
- BCX1812-106 was a large cardiovascular safety study (n=52)
- The study conformed to FDA guidelines for a thorough QTc study
- The study was well conducted, with minimal protocol violations

## CONCLUSIONS

- Peramivir at a therapeutic or supratherapeutic dose was not associated with QTc prolongation or other repolarization abnormalities.
- Pharmacokinetic results at 600 mg were consistent with those previously reported following administration of IV peramivir 8 mg/kg to healthy volunteers<sup>4,5</sup>.
- ECG and safety results were consistent with those previously reported in elderly subjects<sup>1</sup>, subjects with renal impairment<sup>2</sup>, and hospitalized subjects with influenza<sup>3</sup>.
- Peramivir was generally safe and well tolerated.

## ACKNOWLEDGMENTS

The authors acknowledge the study participants and study site personnel at Cetero Research, the study teams at BioCryst and Cardiocore who participated in BCX1812-106, and HHS/BARDA for funding support.

## REFERENCES

- Collis PJ, Harman LA, Kilpatrick JM, et al. A placebo-controlled evaluation of the safety and pharmacokinetics of multiple-dose intravenous administration of peramivir to healthy elderly subjects [Abstract A-1409]. Presented at 47th Annual Meeting ICAAC, 2009.
- Swan S, Marbury T, Smith W, et al. Safety and pharmacokinetics of peramivir following intravenous administration in subjects with renal impairment [Abstract 623]. Presented at 47th Annual Meeting IDSA, 2009.
- Ison MG, McKeer AJ, Hui DS, et al. Safety and efficacy of multiple-day treatment with intravenous peramivir or oral oseltamivir in hospitalized adults with acute influenza [Abstract V-6]. Presented at XI International Symposium on Respiratory Viral Infections, 2009.
- Beigel J, Harman LA, Collis PJ, et al. Pharmacokinetic and safety evaluations of escalating doses of peramivir administered intravenously in healthy volunteers [Abstract A-1408]. Presented at 47th Annual Meeting ICAAC, 2009.
- Centers for Disease Control and Prevention. Emergency use authorization of peramivir IV fact sheet for health care providers. Accessed on May 15, 2010 at [http://www.cdc.gov/h1n1flu/eaupdf/final\\_hcp\\_fact\\_sheet\\_peramivir\\_IV\\_CDC.pdf](http://www.cdc.gov/h1n1flu/eaupdf/final_hcp_fact_sheet_peramivir_IV_CDC.pdf)