CLINICAL STUDY REPORT

PROTOCOL NO. BCX1812-211

U.S. IND NO. 76,350
EUDRACT NO. 2006-005196-17

A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-MASK, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRAMUSCULAR PERAMIVIR IN SUBJECTS WITH UNCOMPLICATED ACUTE INFLUENZA

Report Date: 09 MAR 2009

BioCryst Pharmaceuticals, Inc.
2425 Kildaire Farm Road, Suite 106
Cary, NC 27518
Phone: (919) 859-1302
Fax: (919) 851-1416

1. TITLE PAGE

Protocol Number:	Protocol No. BCX1812-211
Study Title:	A Phase 2, multicenter, randomized, double-mask, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.
IND Number:	U.S. IND No. 76,350 EudraCT No. 2006-005196-17
Investigational Product:	Peramivir (BCX-1812)
Indication Studied:	Uncomplicated Acute Influenza
Sponsor:	BioCryst Pharmaceuticals, Inc. 2190 Parkway Lake Drive Birmingham, AL 35244
Development Phase:	Phase 2
Dates:	
First Subject Randomized:	23 January 2007
Last Subject Completed:	05 September 2007
Sponsor Medical Officer:	W. James Alexander, MD, MPH Clinical Advisor Phone: (919) 859-1302 Fax: (919) 851-1416
Principal Investigator:	Refer to Investigator List
Compliance Statement:	This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and ICH Guidelines. Essential study documents are currently archived in accordance with applicable regulations.
Final Report Date:	09 MAR 2009

1.1. Report Signature Page

BioCryst Pharmaceuticals, Inc.

Reviewed and Approved by:

Alan S. Hollister MD PhD for Dr. Sheridan — 1 July 2010

William P. Sheridan, MD
Chief Medical Officer and Senior Vice President — Date

Reviewed and Approved by:

Elliott T. Berger — 02 JULY 2010

Elliott T. Berger, PhD
Senior Vice President, Regulatory Affairs — Date

2. SYNOPSIS

Sponsor: BioCryst Pharmaceuticals, Inc. **Name of Finished Product:** Peramivir for Intramuscular Injection **Name of Active Ingredient:** Peramivir	Individual Study Table Referring to Part of the Dossier Volume: [x] Page: [x]	(For National Authority Use Only)

Title of Study: A Phase 2, multicenter, randomized, double-mask, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.

Investigator(s): The study involved 151 investigators. Refer to the Investigator List for details.

Study Center(s): Multinational, refer to List of Centers for details.

USA:	81	study centers
Canada:	8	study centers
United Kingdom:	9	study centers
Australia:	12	study centers
Hong Kong:	10	study centers
New Zealand:	7	study centers
South Africa:	24	study centers

Publications: None

Study Period: First Subject Enrolled: 23 January 2007 Last Subject Completed: 05 September 2007	**Phase of Development:** Phase 2

Objectives:

Primary: To evaluate the efficacy of peramivir administered intramuscularly compared with placebo in adult subjects with uncomplicated acute influenza.

Secondary: To evaluate the safety and tolerability of peramivir administered intramuscularly compared with placebo in adult subjects with uncomplicated acute influenza.

Study Design: This was a multinational, randomized, double-mask study comparing the efficacy and safety of peramivir administered intramuscularly versus placebo in adults with uncomplicated acute influenza. Subjects were stratified according to current smoking behavior and were centrally randomized to receive one of three treatments:

Treatment Group 1: Peramivir 150 mg

Treatment Group 2: Peramivir 300 mg

Treatment Group 3: Placebo

Study drug was administered as one 2-mL intramuscular (IM) injection in each gluteal muscle (total of 4 mL injected in divided doses).

At Screening, potential subjects had anterior nasal swabs collected for testing by Rapid Antigen Test (RAT) for influenza A and B. If this test was positive and the subject was enrolled, additional specimens were obtained for isolation and culture of influenza virus and PCR assay. If the initial RAT was negative, the test could be repeated within 1 hour of obtaining a negative result. A second negative RAT would exclude the subject from evaluation for enrollment.

Enrolled subjects recorded the following in a Study Diary:

- Oral temperature measurements taken with an electronic thermometer every 12 hours. Temperature measurements were obtained at least 4 hours after, or immediately before, administration of oral acetaminophen (paracetamol), if applicable.
- Assessment of seven symptoms of influenza on a 4-point severity scale (0, absent; 1, mild; 2, moderate; 3, severe) twice daily through Day 9, then once daily through Day 14.
- Assessment of the ability to perform usual activities, (0–10 on a visual analog scale) once daily through Day 14.
- Doses of antipyretic (acetaminophen/ paracetamol), expectorant, and/or throat lozenges administered each day through Day 14.
- Assessment of injection site discomfort through Day 5.

Following administration of study drug, anterior nasal (bilateral) and posterior pharyngeal specimens (swabs) were collected at Days 2, 3, 5, and 9, for influenza viral culture and PCR assay.

Number of Subjects (Planned and Analyzed):

Planned: Randomized: 300; Completed: 300; Evaluable: 300
Final: Randomized: 344; Completed: 336; Evaluable: 313

Diagnosis and Main Criteria for Inclusion:

Male and female subjects, 18 years of age and older, with symptoms consistent with a clinical diagnosis of uncomplicated acute influenza infection could be screened for enrollment. Subject eligibility was dependent on a positive result obtained from a RAT for influenza A or influenza B at Screening.

Test Product, Dose and Mode of Administration, and Lot Number:

Test Product:	**Dose and Mode:**	**Lot Number:**
Peramivir (BCX-1812), 75 mg/mL	150 or 300 mg, divided dose, IM in the gluteal muscle, bilaterally.	L0104547

Duration of Treatment: The duration of this study was expected to be 6–8 months. Study duration for individual subjects was expected to be up to 14 days (including all visits).

Reference Therapy, Dose and Mode of Administration, and Batch Number:

Placebo (buffered diluent), 2 mL per injection, administered intramuscularly in the gluteal muscle, bilaterally. Lot number L0104083.

Criteria for Evaluation:	
Efficacy:	**Primary End Point:** *Clinical:* Time to alleviation of symptoms. **Secondary End Points:** *Clinical:* Time to resolution of fever. Time to resumption of ability to perform usual activities. *Virologic:* Change (reduction) in influenza virus titer by tissue culture inhibitory dose ($TCID_{50}$/mL).
Safety:	Safety was assessed by periodic physical examinations, vital signs, clinical laboratory tests, electrocardiograms, and occurrence of adverse events.
Statistical Methods:	Descriptive statistical methods were used to summarize the data from this study, with statistical testing utilized for the primary and secondary efficacy endpoints. Unless otherwise noted, all statistical testing was two-sided, and performed using a significance (alpha) level of 0.05. For assessment of the primary efficacy endpoint, the overall significance level was maintained by a Bonferroni adjustment for the planned comparisons between the two active treatment groups and placebo. **Efficacy** The intent-to-treat infected population included all subjects who were randomized, received study drug, and had proven influenza by any one of the following: culture, PCR, or paired serology showing ≥ 4-fold increase in antibody to influenza A or B. The primary efficacy variable was the time to alleviation of symptoms, defined as the start of the time period when all of the seven symptoms assessed were either absent or were present at no more than a mild severity level and remained at that severity status for at least 24 hours. Descriptive statistics for the primary efficacy variable were tabulated by treatment group. Alleviation of symptoms was determined by assessment of symptoms as reported in the Subject Diary. Time to alleviation of symptoms was summarized for each treatment group. Treatment difference was assessed using a Cox Regression model with effects for current smoking behavior and treatment group. Subjects who did not experience alleviation of symptoms were censored at the date of their last assessment. **Safety** Safety analyses were presented for all subjects in the safety population, defined as all randomized subjects who received at least one dose of study drug. Discontinuation of study drug, adverse events, concomitant medications, physical examinations, clinical laboratory test results and vital signs data were summarized by treatment group.

Summary of Results:

Subject Disposition:
Three hundred forty-four subjects had positive RAT results at Screening and were randomized. A total of 342 (99%) subjects received study drug. Influenza was confirmed in 318 (92%) subjects either by PCR assay of nasopharyngeal specimen(s) or by paired serology showing ≥ 4-fold increase in antibody to influenza A or B. Of those subjects randomized, three hundred thirty-six (98%) subjects completed the study and 8 (2%) subjects withdrew prematurely. The overall mean duration of study participation was 14.1 (SD 1.99) days.

Demographics:
The mean age of subjects in this study was 35.5 years with a range of 17 to 92 years. There were 183 female (53%) and 160 male (47%) subjects enrolled. The majority of subjects were White or Caucasian [236 (69%)] with most subjects' ethnicities described as not Hispanic or Latino [323 (94%)]. Most subjects [269 (78%)] were non-smokers. The respective proportions of subjects by the estimated times of onset of symptoms at Screening were 30%, 39% and 31% for the periods 0-24 hours, >24-36 hours, and >36-48 hours. The mean initial composite symptom score (defined as the sum of the 7 symptoms of influenza initially recorded by the subject in the diary) was 14.4 (SD 3.62). The mean height in centimeters was 169.3 (SD 9.49) with a range of 144 to 200 centimeters. The mean weight in kilograms was 78.3 (SD 19.58), with a range of 39 to 141.2 kg. Mean BMI at Screening was 27.2 kg/m^2 (SD 6.10) with a range of 15.7 to 50.2 kg/m^2.

Clinical Efficacy:

Among all subjects with confirmed influenza in the ITTI population, treatment with a single dose of peramivir was associated with non-significant improvements in the median time to alleviation of influenza symptoms of 22.1 hours for the 150 mg peramivir dose group and 18.8 hours for the 300 mg peramivir dose group (p=0.377).

There was a significant difference in the time to fever resolution among subjects in the three treatment groups, and the median time to resolution of fever among subjects treated with 300 mg peramivir (42.9 hours) was significantly lower when compared with placebo treatment (58.1 hours; $p \leq 0.001$).

Treatment with either dose of peramivir was associated with shorter times to resumption of subjects' ability to perform usual activities (medians of 9.2 and 8.3 days for 150 mg peramivir and 300 mg peramivir, respectively) compared with placebo treatment (median of 10.1 days), but these differences were not statistically significant.

Virologic Efficacy:

Treatment with peramivir was associated with a significantly greater decreases in influenza viral titers in nasopharyngeal samples collected at 24 and 48 hours than after placebo treatment. Median decreases from baseline were 1.50 $\log_{10}$ $TCID_{50}$/mL for placebo treatment, 2.00 $\log_{10}$ $TCID_{50}$/mL for peramivir 150 mg treatment, and 2.25 $\log_{10}$ $TCID_{50}$/mL for peramivir 300 mg treatment (p=0.002). At 48 hours after treatment, the median decrease from baseline with peramivir 300 mg treatment (3.25 $\log_{10}$ $TCID_{50}$/mL) was significantly greater than the decrease from baseline after placebo treatment (2.75 $\log_{10}$ $TCID_{50}$/mL) ($p<0.001$).

Safety:
Overall, adverse events occurred with similar frequencies in subjects receiving either peramivir 150 mg (38%), peramivir 300 mg (38%) or placebo (43%), with no apparent difference in the safety profiles of

the peramivir 300 mg treatment and the peramivir 150 mg treatment. The study drug treatments (injections) were generally well tolerated. On the day of treatment, injection site discomfort (self-rated for both injection sites) was rated as severe by 15-18% of subjects who received placebo, by 16-17% of subjects who received peramivir 150 mg, and by 20-22% of subjects who received peramivir 300 mg. At 24 hours after injection, severe discomfort was reported by 0-1% of subjects who received placebo, by 3-4% of subjects who received peramivir 150 mg, and by 2-3% of subjects who received peramivir 300 mg. Two subjects experienced serious adverse events; neither SAE was attributed to study treatment. One of these serious adverse events (meningitis) had a fatal outcome and occurred in a subject who had received peramivir 300 mg approximately 10 days prior to the onset of clinical signs of meningitis. No other adverse events resulted in fatal outcome or were judged to be life-threatening.

Clinical laboratory tests showed no changes of clinical significance among subjects in any of the three treatment groups for clinical chemistry, clinical hematology, or liver function tests; results of monitoring of serum creatine kinase were consistent with intramuscular injection of study drug. Post-treatment monitoring showed no evidence of renal toxicity of peramivir, as assessed by quantitative urine protein determinations or changes in serum creatinine.

Influenza-related complications (otitis, sinusitis, bronchitis, and/or pneumonia) were reported for 18% of all subjects with confirmed influenza; the incidences of any complication among the three treatment groups was placebo - 19%; peramivir 150 mg - 21%; and peramivir 300 mg - 14%.

Conclusions:

Single dose treatment with peramivir provided evidence of activity as an antiviral therapy in adults with acute uncomplicated influenza. Compared with placebo, peramivir treatment was associated with statistically significant decreases in influenza viral titers in nasopharyngeal secretions at 24 and 48 hours after treatment. Clinical efficacy of peramivir was suggested by reductions in the time to alleviation of symptoms of influenza when compared to placebo, but the magnitude of improvement was not statistically significant. In addition, peramivir treatment was associated with shorter times to resolution of fever and resumption of normal activities compared to placebo treatment. Dose responses between the two peramivir regimens were not consistently observed among the various outcome measures assessed.

Peramivir was generally safe and well tolerated and no clinical or laboratory safety concerns were apparent during this study.

Further evaluation of the efficacy and safety of peramivir for treatment of acute influenza is warranted.