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APPLICATION NUMBER:

206426Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	206426
Original Submission Date	21 Dec 2013
Submission Type	505(b)(1) New Drug Application, standard review
SDNs	1, 4, 18, 19
Brand Name	RAPIVAB®
Generic Name	Peramivir
Office of Clinical Pharmacology (OCP) Review Team	Leslie Chinn, Ph.D., Jeffry Florian, Ph.D., Islam Younis, Ph.D.
OCP Division	DCP4
OND Division	Division of Antiviral Products
Applicant	BioCryst Pharmaceuticals, Inc.
Strength and Formulation	10 mg/mL peramivir in 0.9% sodium chloride solution; three vials of 200 mg (20 mL) in a carton
Proposed Dosing Regimen	Single 600 mg dose administered by intravenous infusion for a minimum of 15 minutes
Proposed Indication	Treatment of acute uncomplicated influenza in patients 18 years and older
Related INDs	IND 69038 (IV), IND (b) (4)

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1. EXECUTIVE SUMMARY

Peramivir is an inhibitor of influenza virus neuraminidase (NAI) that prevents the release of new viral particles from infected cells. The proposed indication is for the treatment of acute uncomplicated influenza in adults 18 years and older. The proposed peramivir dose is a single intravenous (IV) administration of 600 mg infused over a minimum of 15 minutes. The product is intended for use in an outpatient setting. Peramivir IV was approved in 2010 in Japan and South Korea as RAPIACTA® and PERAMIFLU®, respectively, for the treatment of influenza. An Emergency Use Authorization was issued by the FDA for the treatment of complicated influenza in Oct 2009; it expired in June 2010. The approved dosage in Japan is either 300 mg in adults or 600 mg in adults at high risk for severe influenza complications, administered as a single intravenous infusion over 15 minutes.

Consideration for approval of this NDA is based on efficacy data from the pivotal Phase 2 trial 0722T0621 as well as pooled safety data from this and other trials, including trials conducted using the peramivir IM formulation. The Clinical Pharmacology Review Team also evaluated data from the supportive Phase 2 trials BCX1812-212 and 0815T0631 , as pharmacodynamic data (i.e. viral IC_{50} values) were collected during these two trials (in addition to the pivotal study) that permitted assessment of the peramivir PK/PD relationship during the Review Team's evaluation of the Applicant's selected dose. A brief description of the efficacy trials evaluated by the Review Team is as follows:

- 0722T0621: randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single administration of peramivir IV 300 and 600 mg, n=298
- 0815T0631: randomized, double-blind, active-controlled trial evaluating the safety and efficacy of a single administration of peramivir IV 300 and 600 mg in comparison to oseltamivir 75 mg BID PO for five days
- BCX1812-212: randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single administration of peramivir IM 600 mg

The clinical pharmacology of peramivir was characterized in three single- and multiple-ascending dose studies, one study in subjects with renal impairment, one study in healthy elderly subjects, four drug-drug interaction studies, one thorough QT (TQT) study, and two relative bioavailability studies. Eight in vitro studies were also conducted: two characterizing plasma protein binding, one assessing the potential for interactions with P-gp, and five investigating the potential for metabolism or metabolizing enzyme interactions via CYP450 enzymes.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP) has determined that there is sufficient clinical pharmacology information provided in this NDA to support a recommendation of approval of a single dose of peramivir 600 mg administered by IV infusion over a minimum of 15 minutes for the treatment of influenza within 48 hours of onset in adult patients, pending the Applicant's agreement to the Clinical Pharmacology Review Team's recommendation for dose reductions to 200 mg and 100 mg in patients with creatinine clearance 30-<50 and <30 mL/min, respectively (refer to Section 2.3.2.5). In addition, the Clinical Pharmacology Review Team also recommends changes to the label as described in Section 3 of this review.

1.2 POST-MARKETING COMMITMENTS OR REQUIREMENTS

None.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The clinical pharmacology of peramivir was characterized during Phase 1 and 2 clinical studies. Data from dedicated clinical pharmacology studies was supplemented by sparse plasma concentration data from clinical trials evaluating the safety and efficacy of peramivir. A brief summary of the clinical pharmacology of peramivir follows:

Dose Selection (for additional details, refer to Section 2.2.4.4)
The Applicant's proposed dose is a single administration of peramivir 600 mg via intravenous infusion over a minimum duration of 15 minutes. PK/PD simulations (based on a PD endpoint of time above viral IC_{50}) determined that the 600 mg dose may provide additional benefit over the 300 mg dose, especially during influenza seasons in which NAI resistance is not prevalent. In addition, although an infusion duration of 30 minutes was used in the pivotal study, population PK simulations estimated a 6% increase in peak plasma concentrations following a 15 minute infusion compared to a 30 minute infusion. The safety of a two-fold increase in peramivir C_{max} was established in the thorough QT study.

Exposure-Response Relationship (for additional details, refer to Section 2.2.4)
Because the difference between peramivir exposures provided by 300 mg vs. 600 mg was greater than the interindividual variability in peramivir exposures at either dose, it was determined that a dose-response analysis was preferable to an exposure-response analysis for this application. Dose-response analyses using the predefined primary efficacy endpoint of time to alleviation of systemic influenza symptoms (TTAS) determined that peramivir confers a shorter TTAS compared to placebo; however, there was no separation between the 300 mg and 600 mg doses of peramivir.

Distribution, Metabolism, and Excretion (for additional details, refer to Section 2.2.5)
Peramivir is administered as an IV infusion. Plasma protein binding is low (<18%) and independent of concentration. Peramivir distributes into extracellular fluid, with a volume of distribution in the range of 300-400 mL/kg). Peramivir is not extensively metabolized in humans and is primarily excreted unchanged in urine via glomerular filtration (in subjects with normal renal function, the mean f_e was 90.4% with a standard deviation of 7.5%).

Intrinsic Factors (for additional details, refer to Section 2.3)
Due to its route of elimination, peramivir clearance is substantially influenced by renal function. Increases in systemic peramivir exposures of 4.1- to 5.5-fold were observed in subjects with moderate and severe renal impairment (defined by the Applicant as CL_{CR} 30-<50 and <30 mL/min, respectively) in a dedicated renal impairment study. The Clinical Pharmacology Review Team therefore recommends reductions in the peramivir dose to 200 mg and 100 mg for patients with CL_{CR} 30-<50 and <30 mL/min, respectively, infused over 15 minutes. Population PK simulations performed by the Review Team indicated that these dose reductions would result in systemic peramivir exposures approximating those observed in patients with normal renal function.

Population PK modeling performed by the Applicant identified body weight and Asian race as having small but significant influences on peramivir volume of distribution (Asian race had a smaller weight-adjusted volume of distribution by approximately 2%), although these factors are not expected to have a clinically meaningful impact.

Extrinsic Factors (for additional details, refer to Section 2.4)
Tobacco use has been identified previously as a baseline factor influencing susceptibility to, severity of, and recovery from influenza. Smoking status was considered during treatment randomization in clinical trials evaluating peramivir efficacy; smoking was included as a covariate, but smokers were not analyzed as a subgroup in efficacy analyses. No drug-drug interactions were observed in clinical studies between peramivir and rimantidine, oseltamivir, levonorgestrel/ethinyl estradiol, or probenecid and no additional drug-drug interactions are expected based upon what is known about the clinical pharmacology of peramivir, including its low potential for inducing or inhibiting CYP450 enzymes or drug transporters such as P-gp.

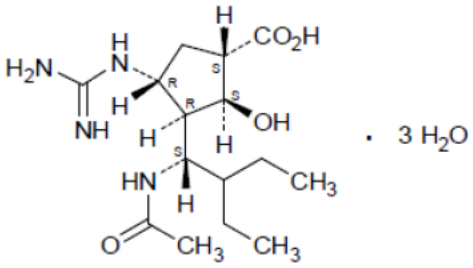
2. QUESTION-BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology review?

The molecular weight of peramivir (formerly referred to as S-021812) is 382.45 Da and the chemical structure is shown in Figure 1.

Figure 1. Chemical structure of peramivir (source: NDA 206426 2.3.S.1)



Peramivir is stable yet sparingly soluble in aqueous solutions in the neutral pH range. As supplied, peramivir injection is a clear, colorless, sterile isotonic solution for IV administration and is prepared by dissolving peramivir in a 0.9% sodium chloride solution to a concentration of 10 mg/mL; pH is adjusted to (b) (4) using (b) (4) HCl or NaOH. (Peramivir injection is further diluted in 0.9% or 0.45% sodium chloride, 5% dextrose, or lactated Ringer's solution to achieve the appropriate dose in a total volume of 100 mL.) The components of peramivir injection are listed in Table 1.

Table 1. Components of peramivir injection (source: NDA 206426 2.3.P.1)

Component	Function	Reference to Quality Standards	Quantitative Composition (Amount/mL)	Amount per Vial (mg)
Peramivir	Active ingredient	In-house	10 mg	200 mg
Sodium Chloride	(b) (4)	USP	9 mg	180 mg
(b) (4) Hydrochloric Acid (b) (4) %	pH adjustment	USP	As required for pH adjustment	As required for pH adjustment
(b) (4) Sodium Hydroxide (b) (4) N	pH adjustment	USP	As required for pH adjustment	As required for pH adjustment
Water for Injection	(b) (4)	USP	(b) (4)	

2.1.2 What are the proposed mechanism and action and therapeutic indication?

Peramivir is a novel inhibitor of influenza viral neuraminidase (NAI) that prevents release of new viral particles from infected cells. The proposed indication is for the treatment of acute uncomplicated influenza in adults. The product is intended for use in an outpatient setting.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosing regimen is a single intravenous infusion of peramivir 600 mg over a minimum of 15 minutes.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical and clinical pharmacology studies used to support dosing or claims?

The relevant clinical studies that were conducted during the peramivir development program are listed in Table 2.

Table 2. List of clinical studies

Phase	Study No.	Objectives	Regimen	Form.	Population (Country)
1	BCX1812-101	PK, safety and tolerability	0.5 mg/kg SD	IV	Healthy subjects (US)
1	BCX1812-102	PK, safety and tolerability	0.5 mg/kg BID for 1 or 10 days	IV	Healthy subjects (US)
1	BCX1812-103	PK, safety and tolerability	1, 2, 4, 8 mg/kg SD 2 mg/kg BID for 1 or 10 days 4 mg/kg BID for 10 days	IV	Healthy subjects (US)
1	BCX1812-104	PK, safety and tolerability	4 mg/kg SD 4 mg/kg BID for 5 or 10 days	IV	Healthy elderly subjects (US)
1	BCX1812-105	PK, safety and tolerability	2 mg/kg SD	IV	Healthy subjects with normal renal function, otherwise healthy subjects with renal impairment (US)
1	BCX1812-108	DDI	600 mg SD with or without 100 mg rimantadine PO	IV	Healthy subjects (US)
1	BCX1812-109	DDI	600 mg SD with or without 75 mg oseltamivir PO	IV	Healthy subjects (US)
1	BCX1812-110	DDI	600 mg SD or placebo with multiple doses of levonorgestrel/ethinyl estradiol 0.15/0.03 mg	IV	Healthy female subjects (US)
1	BCX1812-111	Relative BA,DDI	75, 150, 300 mg SD 150 mg SD (IM) with or without 1 g probenecid PO	IV, IM	Healthy subjects (US)
1	BCX1812-113	Relative BA (crossover)	600 mg SD	IV, IM	Healthy subjects (US)
2	0722T0621	Safety and efficacy	300 or 600 mg SD or placebo	IV	Patients with acute uncomplicated influenza (Japan)
2	BCX1812-212	Safety and efficacy	600 mg SD or placebo	IM	Patients with acute uncomplicated influenza (US, AUS, NZ, ZAF)
3	0815T0631	Safety and efficacy	300 or 600 mg SD or oseltamivir 75 mg BID PO for 5 days	IV	Patients with acute uncomplicated influenza (Japan, S. Korea, Taiwan)

Abbreviations: DDI – drug-drug interaction, BA – bioavailability, SD – single dose, US – United States, AUS – Australia, NZ – New Zealand, ZAF – South Africa

Evaluation of the efficacy of a single dose of peramivir IV 600 mg by the Clinical Pharmacology Review Team focused on the three studies in the peramivir development program for which subject-level IC_{50} values (a baseline factor predictive of NAI antiviral activity) were available. Of these studies, one (0722T0621, considered the pivotal efficacy trial) demonstrated that both the 300 and 600 mg doses of peramivir IV administered within 48 h of onset of illness significantly shortened the time to alleviation of influenza symptoms compared to placebo (Table 3). Similarly, when the dose groups are combined, there is a statistically significant improvement over placebo in terms of time to alleviation of influenza symptoms (one-sided p-value of 0.0010 for the S-021812 consolidated group, Table 3).

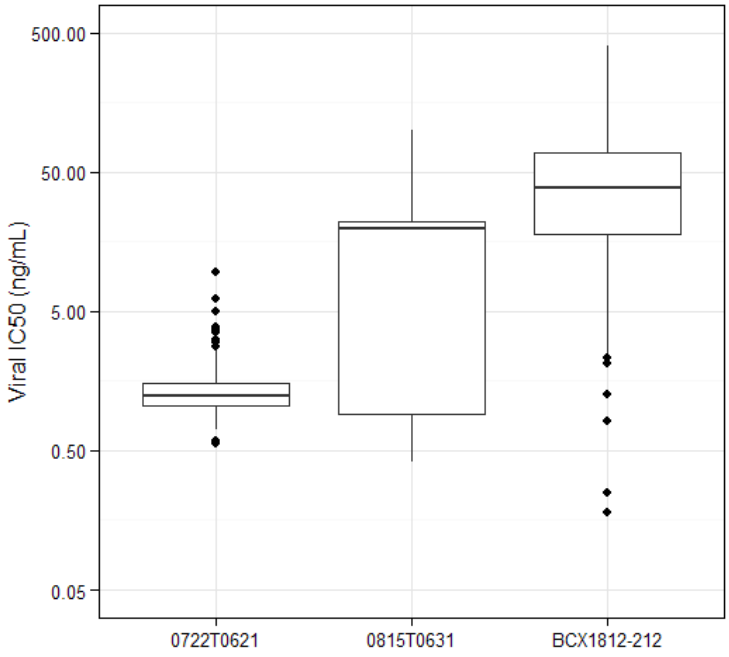
Table 3. Summary of 0722T0621 primary endpoint (source: 0722T0621 CSR Table 15)

	S-021812 consolidated group N = 196	**300 mg group N = 99**	**600 mg group N = 97**	**Placebo group N = 100**
Median (hrs)		59.1	59.9	81.8
(95% Confidence Interval)		(50.9, 72.4)	(54.4, 68.1)	(68.0, 101.5)
Improvement over Placebo (hrs)		-22.7	-21.9	—
Cox proportional hazards model				
Estimate		-0.3837	-0.4062	—
SE		0.1472	0.1479	—
Hazard ratio		0.681	0.666	—
(95% Confidence Interval)		(0.511, 0.909)	(0.499, 0.890)	—
Chi-square test statistic	9.5277	6.7916	7.5463	—
DF	1	1	1	—
p-value (one-sided	0.0010*	0.0046*	0.0030*	—
Adjusted p-value (one-sided)	---	0.0046*	0.0046*	—

Covariates: Current smoking behavior, Composite symptom scores at baseline
Adjusted p-value: Determined by Hochberg method
*: Statistical significance; p-value or Adjusted p-value (one-sided) <0.025

The other two efficacy studies evaluated in this review (BCX1812-212 and 0815T0631) were conducted during the 2008/2009 influenza season during which there was widespread NAI resistance due to the H275Y mutation in the circulating H1N1 strain, as evidenced by the higher median IC_{50} values in these studies compared to 0722T0621 (Figure 2), which was conducted during the 2007/2008 influenza season. Although neither of these studies demonstrated that peramivir significantly shortened the duration of influenza symptoms compared to placebo (indeed, study 0815T0631 lacked a placebo control), they provide supportive evidence for the use of parenteral peramivir to treat uncomplicated influenza.

Figure 2. Peramivir IC_{50} values by study (source: Reviewer's analysis of BCX1812-212 GPVDATA.xpt, 0722T0621 GPVDATA.xpt, 0815T0631 GPVDATA.xpt)



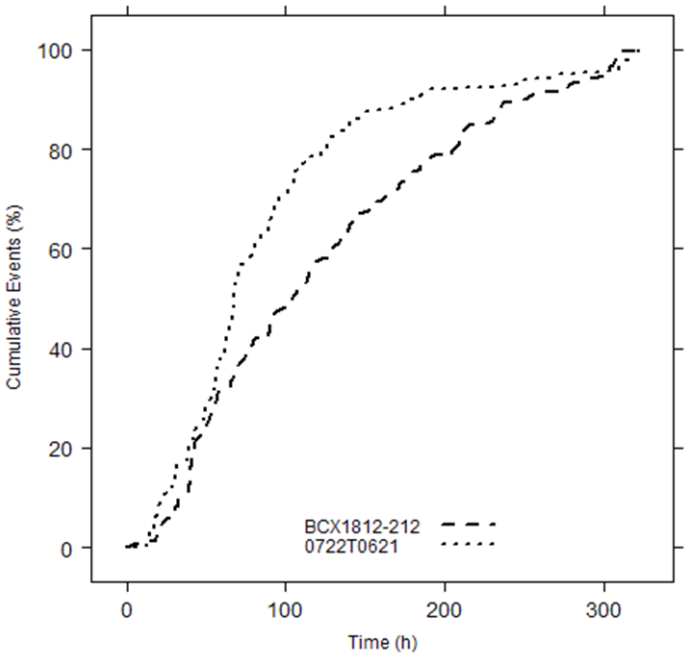
2.2.2 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary response endpoint used during peramivir development program was the "time to alleviation of systemic symptoms" (TTAS), also called "duration of influenza." TTAS was a composite score based on the time to alleviation of seven influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, aches or pains of the muscles or joints, fatigue) as recorded by the patient twice daily from Screening until Day 9 and once daily from Days 10-14 in a diary. Individual symptoms were graded on a scale of 0 (absent) to 3 (severe); TTAS was defined as the timepoint at which all seven symptoms showed a score of 0 or 1. The composite score at baseline was taken into consideration during treatment randomization.

Similar primary endpoints have been used during efficacy trials of drugs for the treatment of acute uncomplicated influenza (*FDA Guidance for Industry: Influenza*, April 2011), including the neuraminidase inhibitor oseltamivir (Tamiflu®, approved by the FDA in 1999). However, due to the subjective nature of patient-assessed outcomes, more objective measures (e.g. body temperature, viral shedding) are used as secondary endpoints in addition to patient-reported secondary endpoints such as time to return to normal activity and the individual symptom scores that comprise TTAS. Note that virologic endpoints are not considered appropriate primary endpoints for the treatment of acute uncomplicated influenza in part because the relationship between the magnitude and timing of reductions in viral load has not been shown to reliably predict clinical benefit to a patient (*FDA Guidance for Industry: Influenza*).

The reproducibility of findings using TTAS as the primary endpoint is likely hindered by the extent of variability in this endpoint across populations and/or between influenza seasons, as is apparent in a comparison of TTAS in the placebo groups in 0722T0621, a study conducted in Japan during the 2007-2008 influenza season, and BCX1812-212, a study conducted in the US, Australia, New Zealand, and South Africa during the 2008-2009 season (Figure 3).

Figure 3. Cumulative distribution of TTAS in placebo groups (source: Reviewer's analysis of 0722T0621 and BCX1812-212 adtte.xpt)



2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Quantification of peramivir in plasma and urine is appropriate to assess the pharmacokinetics of peramivir because peramivir is predominantly excreted unchanged in the urine. Plasma and urine were assessed for the presence of metabolites in two non-IND studies (0712T0611 and S-021812-PR-062-C) following single or multiple doses of peramivir IV to healthy subjects; the Applicant reports that no metabolites were detected in plasma or urine. The apparent absence of metabolism is supported by the results of the renal impairment study (BCX1812-105), in which the fraction of peramivir dose excreted ranged from 76-97% (mean: 90.4%, standard deviation: 7.5%) by 168 h postdose in subjects with normal renal function (CL_{CR} >80 mL/min, n=6).

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The Applicant evaluated the efficacy of a single dose of two dose levels (300 and 600 mg) of peramivir IV in the pivotal trial 0722T0621 and the supportive trial 0815T0631. Because the extent of interindividual variability in peramivir PK is low, the difference between peramivir

exposures provided by 300 mg vs. 600 mg was greater than the interindividual variability in peramivir exposures at either dose. It is unlikely that an exposure-response relationship would exist in the absence of a dose-response relationship for a small molecule drug; therefore, the Clinical Pharmacology Review team determined that a dose-response analysis was preferable to an exposure-response analysis for this Application.

A cumulative distribution curve (similar to a survival analysis) was used to evaluate the peramivir dose-response relationship for the TTAS endpoint over time (Figure 4). While peramivir appears to confer a shorter TTAS compared to placebo (black dashed line), there is no separation between the 300 mg or 600 mg doses of peramivir (orange and red lines, respectively) based on visual inspection. A similar analysis of the TTAS endpoint in the supportive study 0815T0631 suggests that single doses of either the 300 and 600 mg doses of peramivir performed similarly to five days of oseltamivir 75 mg BID (Figure 5), although these results should be interpreted with caution (particularly in the absence of a placebo) because this study was performed during the 2008-2009 influenza season in which there was widespread NAI resistance.

Figure 4. Cumulative distribution of TTAS in 0722T0621 (source: Reviewer's analysis of 0722T0621 adtte.xpt)

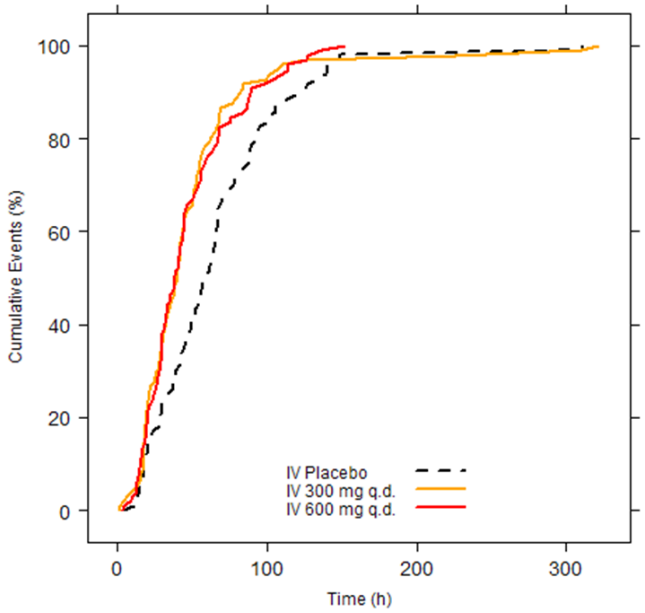
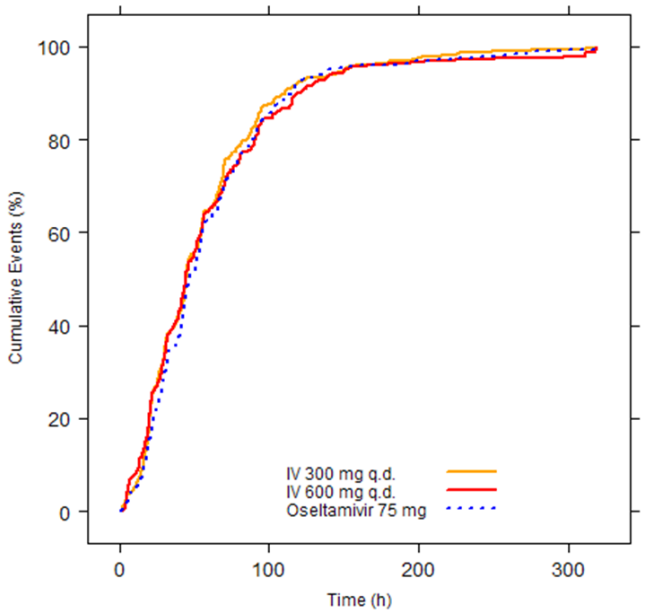


Figure 5. Cumulative distribution of TTAS in 0815T0631 (source: Reviewer's analysis of 0815T0631 adtte.xpt)



Based on an assessment of the cumulative distribution curves for the pivotal efficacy study as well as a supportive study, there does not appear to be a relationship between peramivir dose (300 mg vs. 600 mg) and the primary efficacy endpoint TTAS.

The relationship between peramivir dose and the time to resolution of fever (TTRF), a clinically meaningful and measurable secondary endpoint, was also evaluated. Visual inspection suggested that peramivir IV 600 mg conferred a slightly shorter TTRF compared to the 300 mg dose in study 0722T0621 (Figure 6), but the cumulative distributions of TTRF appeared to be similar for both doses of peramivir (as well as oseltamivir) in study 0815T0631 (Figure 7).

Figure 6. Cumulative distribution of TTRF in 0722T0621 (source: Reviewer's analysis of 0722T0621 adtte.xpt)

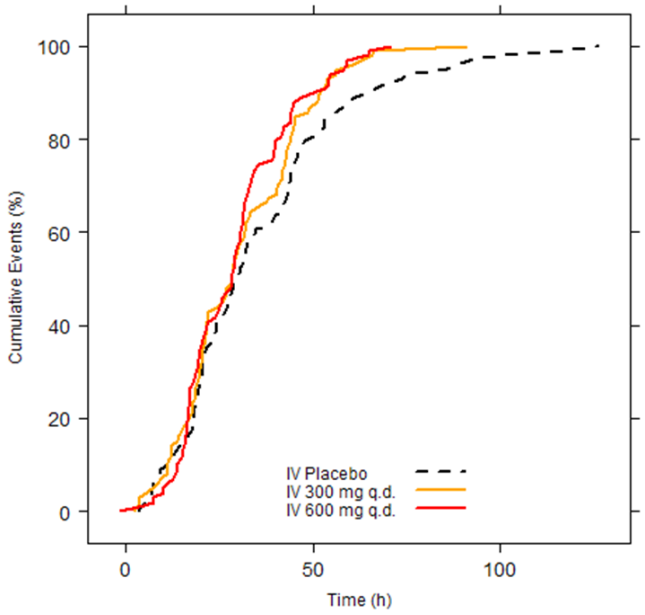
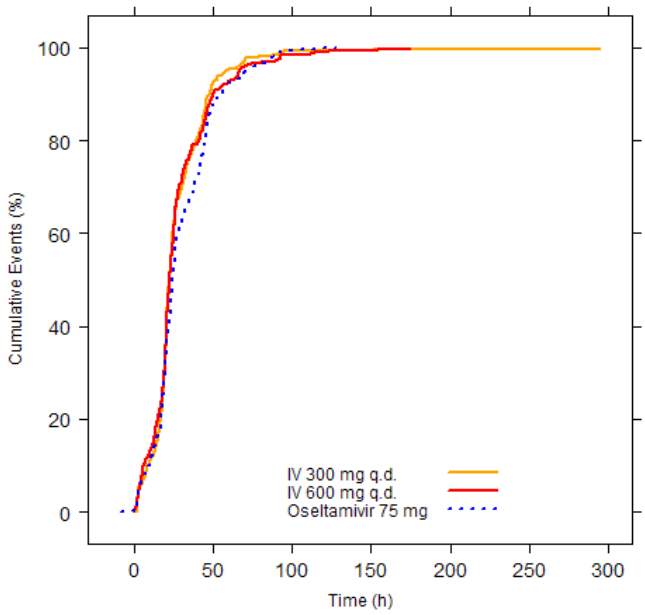


Figure 7. Cumulative distribution of TTRF in 0815T0631 (source: Reviewer's analysis of 0815T0631 adtte.xpt)



There are insufficient data from the three efficacy studies evaluated to perform a dose-response analysis in patients with influenza B infection or in patients infected with influenza A/H1N1 containing the H275Y neuraminidase mutation.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The dose- and exposure-response relationships for safety were not evaluated. The only adverse reactions that occurred more frequently in the treatment arm compared to placebo and at a rate of at least 2% were decreased neutrophil count (5.7% in the peramivir arm vs. 0% in the placebo arm), white blood cells in urine (2.7% vs. 1.8%), increased blood creatinine phosphokinase (2.1% vs. 0.5%), and increased lymphocyte percentage (2.1% vs. 1.1%). All of these adverse reactions were lab abnormalities and were not considered to be clinically significant, particularly as the proposed peramivir IV regimen consists of only a single administration (please refer to the review by Dr. Pete Miele).

2.2.4.3 Does this drug prolong the QT or QTc interval?

No significant QTc prolongation effect of a single dose of peramivir IV 600 or 1200 mg was detected in the placebo- and positive-controlled crossover TQT study (BCX1812-106) conducted in healthy volunteers. Following the supratherapeutic 1200 mg dose, the mean peramivir C_{max} and AUC_{inf} were 93,206 ng/mL and 199,719 ng.h/mL, respectively, approximately 2-fold of the therapeutic dose of 600 mg. This study was evaluated under IND 69038 by the FDA CDER Interdisciplinary Review Team for QT Studies (review filed in DARRTS on 10 June 2010).

2.2.4.4 Are the dose and dosing regimen selected by the Applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Dose selection

While two doses of peramivir IV, 300 mg and 600 mg, were evaluated in the pivotal placebo-controlled study 0722T0621 and the supportive active-controlled study 0815T0631, the Applicant is proposing that the dose of 600 mg be approved for the treatment of uncomplicated influenza in adults. In the absence of a relationship between dose and the primary endpoint TTAS, the Applicant cites virologic and PK/PD evidence to support the 600 mg dose over the 300 mg dose.

The Review Team performed independent simulations using the Applicant's PK/PD model (using a simple two-compartment model with linear elimination to describe PK, followed by a baseline hazard model [modeled as a Gompertz relationship] incorporating drug effect to describe PD) in order to assess the predicted post-infusion time that peramivir plasma concentrations were above IC_{50} in a population (n=10,000) with baseline characteristics and IC_{50} values randomly sampled from the three efficacy trials evaluated. Statistical significance of time above IC_{50} values between treatments was not assessed as it could be influenced by the number of patients in a simulation. For further details on the model, please refer to the Pharmacometrics Review.

As expected, PK/PD simulations demonstrated that the 600 mg dose was correlated with a longer time above IC_{50}, with a median time above IC_{50} of 29 and 39 h for the 300 and 600 mg doses, respectively, simulated with IC_{50} values across all three studies (Table 4). However, the higher dose did not confer an improvement when simulations were performed using IC_{50} values sampled from BCX1812-212, which was conducted during a season when the NAI-resistant H1N1 H275Y strain was widespread, with median time above IC_{50} values of 20 and 22 h for the

300 and 600 mg doses, respectively. This result is not unexpected as the distribution of IC_{50} values in BCX1812-212 was the highest of the three efficacy studies evaluated (Figure 8) and was shifted rightward by the IC_{50} values associated with the H1N1 H275Y strain (Figure 9).

Table 4. Simulated PD results (target time above IC_{50}) by study and viral subtype for a single dose of peramivir IV 300 or 600 mg infused over 15 min (based on BCX1812-PPK-1)

IC_{50} population	**Number of subjects**	**Median IC_{50} (IQR) (ng/mL)**	**Simulated median time above IC_{50} (IQR) (h)**	
			300 mg	**600 mg**
All studies	1723	19 (1.0, 23)	29 (20, 73)	39 (28, 80)
0722T0621	296	1.2 (1.1, 1.5)	73 (65, 81)	84 (77, 91)
0815T0631	1093	20 (0.92, 22)	27 (20, 74)	38 (29, 74)
BCX1812-212	334	39 (17, 69)	20 (20, 26)	22 (20, 39)
H1N1[1]	846	21 (19, 23)	22 (20, 32)	34 (28, 44)
H1N1 H275Y	230	51 (32, 79)	20 (20, 20)	20 (20, 27)
H3N2	444	0.84 (0.76, 0.98)	80 (72, 87)	89 (83, 95)
B	127	3.6 (3.5, 4.3)	52 (44, 59)	65 (57, 73)

[1] Includes H1N1 H275Y in studies in which resistance mutation genotyping was not performed (i.e. 0722T0621 and 0815T0631)

Figure 8. Distribution of IC_{50} values by study (source: Reviewer's analysis of BCX1812-212, 0722T0621, 0815T0631 GPVDATA.xpt)

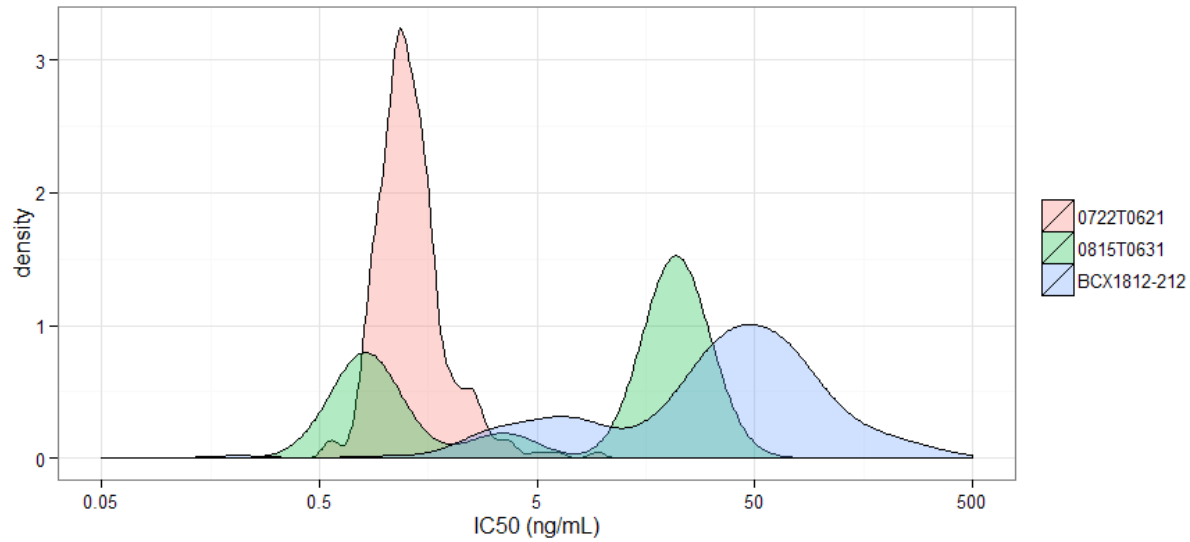
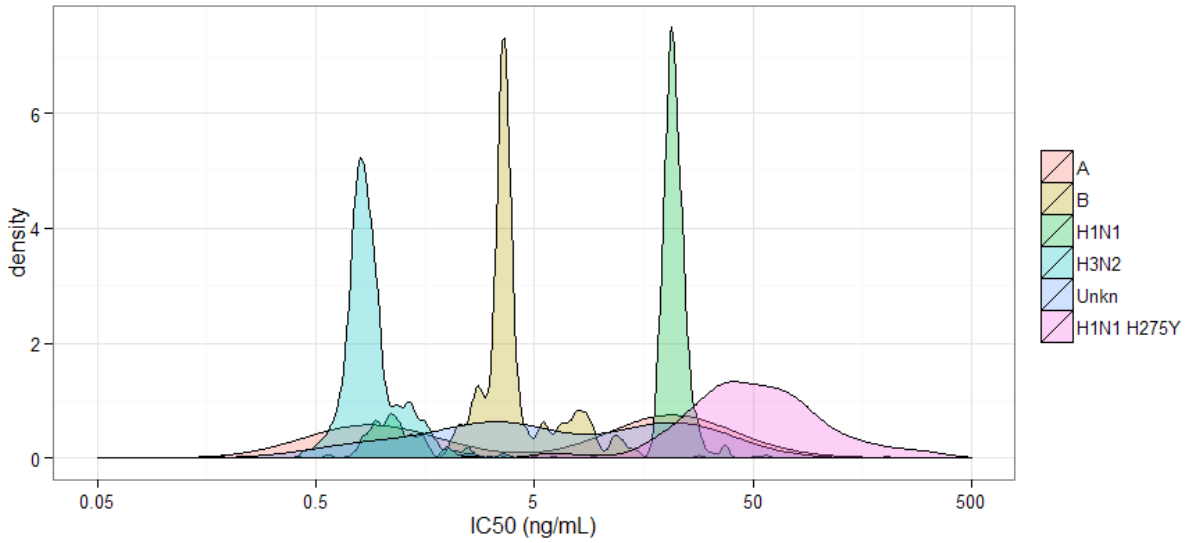


Figure 9. Distribution of IC_{50} values by influenza strain and subtype (source: Reviewer's analysis of BCX1812-212, 0722T0621, 0815T0631 GPVDATA.xpt)



The simulations performed by the Review Team demonstrate that the 600 mg dose is predicted to provide systemic peramivir exposures that are above the IC_{50} for a longer period of time, on average. While the clinical relevance of this PK/PD analysis has not been established, it is plausible that the duration of time above IC_{50} could be associated with antiviral activity in a greater percentage of patients at the 600 mg dose compared to the 300 mg dose, especially during an influenza season in which NAI resistance is intermediate (i.e. there is some degree of NAI resistance, but the circulating influenza strains remain susceptible to NAIs). The added benefit of the 600 mg dose compared to the 300 mg dose may be lost in seasons in which viral IC_{50} values are very low (circulating strains are highly susceptible to NAIs, in which case both doses will be effective) or very high (circulating strains are highly resistant to NAIs, in which case neither dose will be effective). These simulations, in addition to the favorable safety profile of a single dose of peramivir IV regardless of dose level, support selection of the 600 mg dose of peramivir IV.

Infusion duration

The proposed minimum infusion duration time is 15 minutes; however, a 30 minute infusion duration time was used in studies 0722T0621, 0815T0631, and BCX1812-212. As increased maximum concentrations could be expected with a shortened infusion duration, simulations were performed to generate C_{max} values. Predicted peramivir C_{max} values (mean ± SD) for an infusion duration of 15 and 30 minutes were 46,230 ± 10,530 and 43,490 ± 9,793, respectively. These predictions are comparable between infusion durations and are similar to observed C_{max} values; therefore, a minimum infusion duration of 15 minutes appears to be reasonable from a clinical pharmacology perspective.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single- and multiple-dose PK parameters?

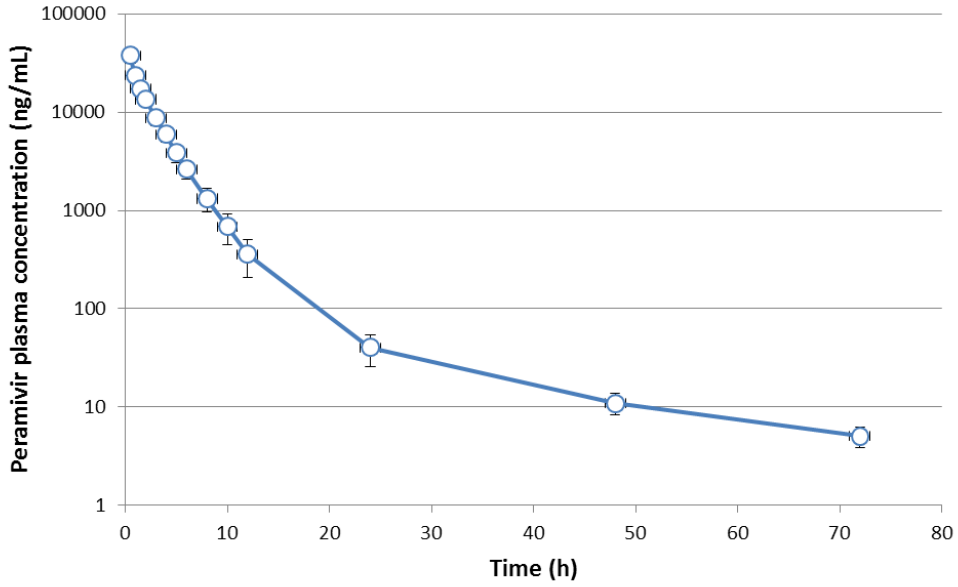
Following administration of a single intravenous dose of peramivir to healthy volunteers, peramivir was eliminated in a multi-exponential fashion with a terminal elimination half-life of approximately 20 hours. Peramivir PK was similar upon single or multiple dosing in subjects with normal renal function. Following multiple days of QD or BID administration, substantial accumulation was not observed; steady-state was reached within 48 h (BCX1812-103). The PK parameters of a single dose of peramivir IV 600 mg (30 min duration) in healthy subjects from the peramivir alone arm of two drug-drug interaction studies are listed in Table 5 (the PK of multiple administrations of 600 mg were not assessed) and a representative concentration-time profile is displayed in Figure 10.

Table 5. Peramivir PK parameters after a single dose of peramivir IV 600 mg (source: BCX1812-108 CSR Table 4, BCX1812-109 CSR Table 6)

Mean (SD)	**BCX1812-108**	**BCX1812-109**
C_{max} (ng/mL)	37,680 (7,819)	37,230 (7,045)
T_{max}[1] (h)	0.5	0.5
AUC_{24} (ng.h/mL)	80,230 (12,450)	89,230 (12,950)
AUC_{inf} (ng.h/mL)	81,170 (12,570)	89,380 (12,990)
CL (mL/h)	7,575 (1,284)	6,854 (1,024)

[1] Median

Figure 10. Mean ± SD peramivir concentration-time profile (source: BCX1812-108 PK data)



2.2.5.2 How does the PK of the drug and its active metabolites in healthy volunteers compare to that in patients?

Based on population PK modeling conducted by the Applicant during Phase 2 (S-021812-CB-077-C), peramivir clearance was slightly faster in patients compared to healthy subjects (mean

peramivir CL: 6.78 and 6.18 L/h in patients and healthy subjects, respectively) and volume was comparable between patients and healthy subjects (mean peramivir V_{ss}: 17.28 and 17.19 L in patients and healthy subjects, respectively). Overall, plasma concentrations were comparable between patients and healthy subjects and the minor differences identified by population PK analyses are not expected to be clinically relevant.

2.2.5.3 What are the characteristics of drug distribution?

In vitro, human plasma protein binding was determined to be low (<18%) across a range of peramivir concentrations (10-1000 ng/mL) with no partitioning into red blood cells (Study DM99362). In plasma samples (collected predose) from subjects with normal renal function or mild to severe renal impairment to which peramivir was added, plasma protein binding ranged from 0-4.9% (BCX1812-105).

Population PK estimates of the volume of distribution were in the range of 300-400 mL/kg, indicating extensive distribution into extracellular fluid.

2.2.5.4 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

A mass balance study was not conducted; however, quantification of peramivir in urine in several clinical studies indicates that peramivir is predominantly excreted via the renal route, with the fraction of peramivir dose excreted (f_e) ranging from 76-97% (mean ± SD: 90.4 ± 7.5%) in seven days after a single administration of peramivir IV to subjects with normal renal function (BCX1812-105).

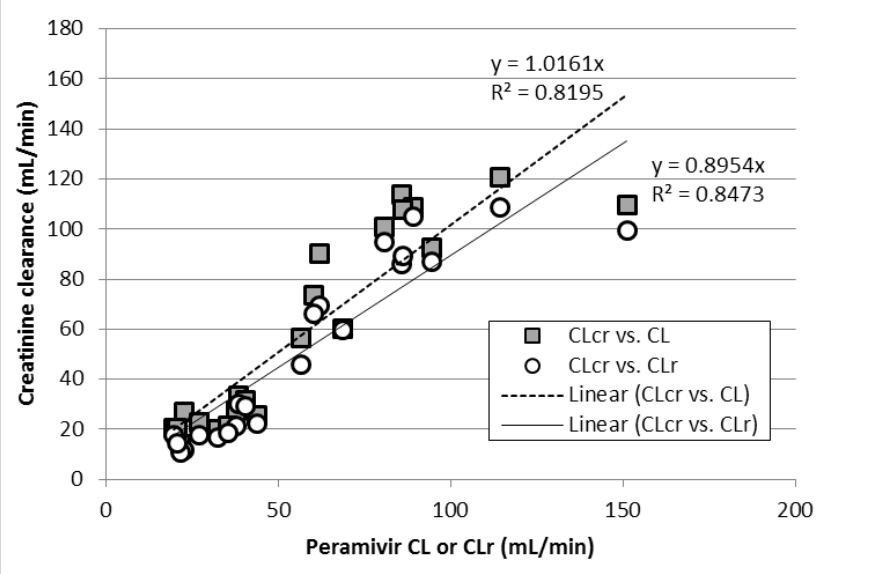
2.2.5.5 What are the characteristics of drug metabolism?

Peramivir is not extensively metabolized in humans. Plasma and urine were assessed for the presence of metabolites in two non-IND studies (0712T0611 and S-021812-PR-062-C) following single or multiple doses of peramivir IV to healthy subjects; the Applicant reports that no metabolites (including the acyl glucuronide metabolite tentatively associated with renal toxicity in nonclinical studies) were detected in plasma or urine. In an in vitro study (DM98357) conducted using pooled human hepatic S9 fractions, a metabolite (peramivir oxidized at the cyclopental ring) was identified at low concentrations (≤4%).

2.2.5.6 What are the characteristics of drug excretion?

Peramivir is primarily excreted unchanged in the urine. The fraction of the peramivir dose excreted ranged from 76-97% (mean: 90.4%, standard deviation: 7.5%) in seven days after a single administration of peramivir IV to subjects with normal renal function (CL_{CR} >80 mL/min, n=6, BCX1812-105). Total clearance and renal clearance were both correlated with creatinine clearance, with correlation coefficients of greater than 0.8 (Figure 10). The slope of the linear relationship between renal clearance and creatinine clearance was 0.9, suggesting that peramivir is primarily eliminated via glomerular filtration (i.e. active tubular secretion and/or reabsorption do not appear to substantially contribute to peramivir elimination).

Figure 11. Relationship between CL_{CR} and peramivir CL and CL_R (source: BCX1812-105 CSR Tables PKT3 and PKT4)



Following the end of infusion, peramivir exhibits multi-exponential decay with a terminal elimination half-life of approximately 20 h.

2.2.5.7 Based on the PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Peramivir exposures increased proportionally with dose (following a single dose) over the range of IV doses evaluated in the development program (50-1200 mg).

2.2.5.8 How do the PK parameters change with time following multiple dosing?

Twice-daily dosing of peramivir IV 2 or 4 mg/kg BID resulted in comparable pharmacokinetic parameters on Days 1 and 10, suggesting minimal accumulation (Day10:Day 1 ratios of C_{max} and AUC were 122% and 93.8%, respectively) with multiple dosing in subjects with normal renal function (study BCX1812-103). Accumulation may be expected to occur upon multiple daily administrations of peramivir in subjects with impaired renal function (see Section 2.3.2.5 for further discussion).

2.2.5.9 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Overall, interindividual variability in peramivir PK parameters was limited, with CVs of approximately 15-20%. The major causes of variability (identified in population PK analyses performed by the Applicant [BCX1812-PPK-1]) include body weight and Asian race for volume of distribution (with Asians having a slightly lower [<2%] weight-adjusted volume of distribution) and creatinine clearance for the elimination rate constant.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on pharmacodynamics? What dosage regimen adjustments are recommended for each of these subgroups, if any?

Due to the substantial influence of renal function on systemic peramivir exposures, the Clinical Pharmacology Review Team recommends a dose reduction to 200 and 100 mg in patients creatinine clearance 30 to <50 mL/min and <30 mL/min, respectively. While higher peramivir exposures are not expected to be detrimental to efficacy, the safety of exposures in the range predicted following a single 600 mg dose in patients with creatinine clearance below 50 mL/min has not been established (refer to Section 2.3.2.5 of this review).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Peramivir PK was assessed in healthy elderly subjects following one or 10 days of peramivir IV 4 mg/kg BID (BCX1812-104). In comparison to healthy non-elderly subjects (BCX1812-103), mean AUC values were approximately 30% higher, while mean C_{max} values were comparable (Table 6). The increase in systemic exposures is attributed to slower clearance due to natural decreases in renal function with age. No dose adjustment is recommended in elderly patients.

Table 6. Key peramivir PK parameters from elderly and non-elderly subjects (source: BCX1812-104 CSR Table 1 and BCX1812-103 CSR)

Days of dosing (4 mg/kg BID)	C_{max} (ng/mL)	AUC_{12h} (ng h/mL)	CL (mL/min)
Non-elderly (BCX1812-103)			
1	20490 (3908)	47800 (4690)	106 (6.77)
10	24750 (3742)	43600 (6390)	109 (12.3)
Elderly (BCX1812-104)			
1	22647.5 (4823)	61334.0 (8793)	-
5	22608.3 (4910)	70465.4 (12236)	79.5 (13.1)
10	22933.3 (2951)	61572.3 (8564)	77.7 (15.4)

2.3.2.2 Pediatrics

A pediatric indication is not being sought in the current application.

2.3.2.3 Gender

In population PK analyses, gender (in addition to body weight) was found to be a statistically significant covariate for volume of distribution; however, the impact of gender on systemic peramivir exposures was not observed to be, and is not anticipated to be, clinically meaningful and no dose adjustment is recommended based on gender.

2.3.2.4 Race

A cross-study comparison of systemic clearance performed by the Applicant suggested that there were no obvious differences in the point estimate or variability in clearance across the dose ranges evaluated in US and Japanese studies, although Asian race (in addition to body weight) was found to be a statistically significant covariate for volume of distribution in population PK analyses (in a population PK analysis, Asian race had a smaller weight-adjusted volume of distribution by approximately 2%). However, the impact of race on systemic peramivir exposures was not observed to be, and is not anticipated to be, clinically meaningful and no dose adjustment is recommended based on race.

2.3.2.5 Renal impairment

Peramivir PK was assessed in subjects with normal renal function (defined by the Applicant as CL_{CR} >80 mL/min); mild, moderate, or severe renal impairment (defined by the Applicant as CL_{CR} 50-80, 30-<50, or <30 mL/min, respectively); or end-stage renal disease (evaluated both before and after hemodialysis) following a single dose of peramivir IV 2 mg/kg (BCX1812-105). An a priori dose reduction was implemented based on the characterization of renal excretion as the primary route of peramivir elimination. While C_{max} was not substantially affected by renal dysfunction, the mean peramivir AUC_{inf} values were approximately 1.4-, 4.1, and 5.5-fold higher in subjects with mild, moderate, or severe renal impairment (as defined by the Applicant) compared to subjects with normal renal function (Table 7); with increasing renal dysfunction there was a corresponding decrease in clearance, as was evident from an assessment of the amount of peramivir excreted in urine over time.

Table 7. Statistical comparison of peramivir plasma PK between renal function groups (source: BCX1812-105 CSR Table 5) (note: comparisons presented in the table are based on 2 mg/kg dosing and not fixed dosing)

Parameter	Renal Group	N	GLS Mean[1]	Pair	Ratio[2] (%)	90% CI[3] (%)
C_{max} (ng/mL)	Normal	6	12,500			
	Mild	5	12,000	Mild/Normal	96.0	(73.3 – 125.9)
	Moderate	6	13,200	Moderate/Normal	105.6	(81.6 – 136.6)
	Severe	5	12,900	Severe/Normal	103.3	(78.8 – 135.4)
	ESRD, Dose 1	6	10,700	ESRD, Dose1/Normal	85.6	(66.1 – 110.7)
	ESRD, Dose 2	6	15,100	ESRD, Dose2/Normal	120.4	(93.0 – 155.9)
$AUC_{0\text{-last}}$ (ng*h/mL)	Normal	6	25,800			
	Mild	5	33,100	Mild/Normal	128.1	(98.7 – 166.3)
	Moderate	6	104,000	Moderate/Normal	401.6	(313.2 – 514.8)
	Severe	5	131,000	Severe/Normal	508.4	(391.7 – 659.8)
$AUC_{0-\infty}$ (ng*h/mL)	Normal	6	25,900			
	Mild	5	33,100	Mild/Normal	128.0	(98.6 – 166.2)
	Moderate	6	104,000	Moderate/Normal	401.8	(313.3 – 515.2)
	Severe	5	132,000	Severe/Normal	511.7	(394.2 – 664.2)

[1] Geometric least squares mean.
[2] Ratio of GLS means.
[3] 90% confidence interval around the ratio of GLS means
Log transformed PK parameters were fitted on an ANOVA model with cohort as fixed effect.
Subjects 1001 (mild renal impairment) and 1002 (severe renal impairment) are excluded as the actual duration of infusion was longer than 15 minutes due to pump malfunction.
Source: Table PKT5.

The Review Team conducted population PK simulations using the Applicant's model based on data from Phase 1 and 2, including data from the renal impairment study, which is further described in the Pharmacometrics Review. Estimates of AUC following a single dose of peramivir IV 600 mg infused over 15 minutes were 1.3-, 2.8-, and 6.4-fold higher in patients with mild, moderate, or severe renal impairment, respectively, compared to exposures in patients with normal renal function. These findings are consistent with the Applicant's simulations. (Note that simulations were not performed for patients with ESRD because a population PK model was not developed for this subpopulation.) As a point of reference, the highest exposures observed so far (mean AUC of 199,719 ng.h/mL in the TQT study BCX1812-106) represented only a two-fold increase in anticipated clinical exposures.

The Review Team considered five options for peramivir dosing for patients with creatinine clearance below 50 mL/min, which are outlined in Table 9; the model-predicted exposures are listed in Table 8.

Table 8. Options for peramivir dosing in patients with renal impairment

Method	Justification	Proposed Dose (mg)	
		30-<50 mL/min	<30 mL/min
No dose reduction	No apparent clinical safety signals; the proposed regimen is only a single dose; ability to assess renal function may be limited in an outpatient setting	600	600
Follow traditional renal impairment dosing for renally excreted drugs (½ and ¼ dose for moderate and severe RI, respectively)	Regulatory precedence (similar dose reductions are recommended for pregabalin, cefepime, doripenem)	300	150
Exposure-match to 600 mg in subjects with normal renal function	The safety and efficacy of these exposures has been characterized in patients with normal renal function	200	100
Exposure-match as above but consider dosing increment	Peramivir is supplied as 200 mg vials and using doses that are multiples of 200 mg would increase the convenience of administration	200	200
Include the equation for peramivir CL in the label	Health care providers will have the ability to precisely dose patients	-	-

Table 9. Predicted systemic peramivir exposure in patients with renal impairment **(source: BCX1812-105 CSR Table 7 and population PK simulations based on model from** S-021812-CB-137-C**)**

Source	Population	Dose (mg)	Median AUC (ng.h/mL)	IQR (ng.h/mL)
Observed	0722T0621 [pivotal efficacy trial	600	78,720	73,650-84,880
	BCX1812-106 [TQT study]	600	97,920	86,200-107,400
		1200	196,200	181,100-199,700
Observed	BCX1812-105 Normal renal function (CL_{CR} ≥80 mL/min)	2 mg/kg[b]	92,520	88,560-97,790
	Mild renal impairment (CL_{CR} 50 to <80 mL/min)	2 mg/kg[b]	135,100	116,600-157,000
	Moderate renal impairment (CL_{CR} 30 to <50 mL/min)	2 mg/kg[b]	373,600	331,800-442,900
	Severe renal impairment (CL_{CR} 10 to <30 mL/min)	2 mg/kg[b]	483,500	446,800-649,400
Simulated	Normal renal function (CL_{CR} ≥80 mL/min)	600	92,650	75,373-113,596
	Mild renal impairment (CL_{CR} 50 to <80 mL/min)	600	124,937	156,014-194,143
		400	83,291	104,010-129,429
	Moderate renal impairment (CL_{CR} 30 to <50 mL/min)	600	259,202	207,134-320,564
		300	129,601	103,567-160,282
		200	86,401	69,045-106,857
	Severe renal impairment (CL_{CR} 10 to <30 mL/min)	600	594,796	426,273-879,192
		200	198,265	142,091-293,064
		150	148,699	106,568-219,798
		100	99,133	71,045-146,532

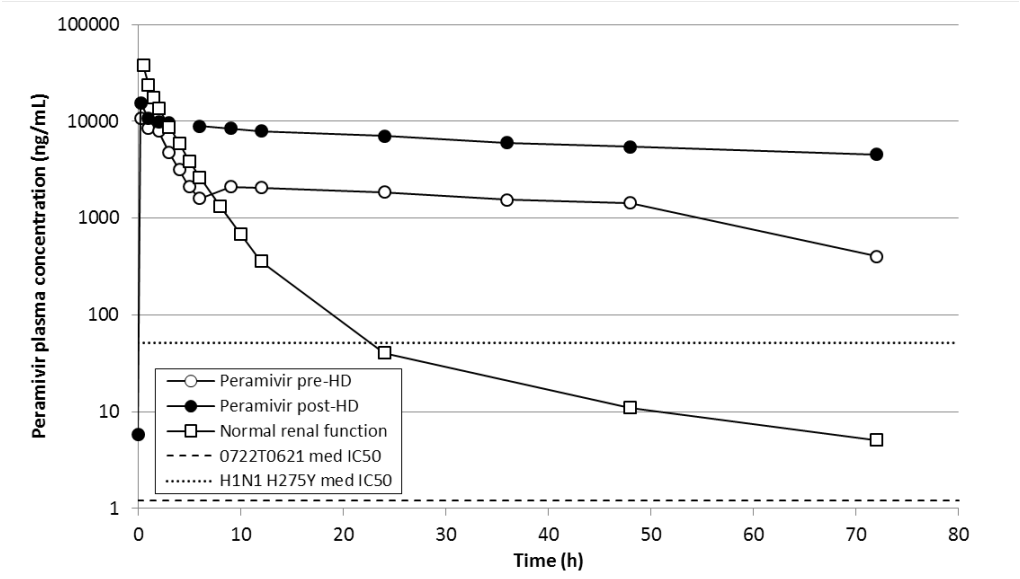
[1] The Applicant's categorization of renal function based on creatinine clearance was used
[2] BCX1812-105

The Clinical Pharmacology Review Team evaluated the potential risks and benefits of each possible option and ultimately elected to match exposures to 600 mg in patients with normal renal function without regard for dosing increment. Selection of this approach should generally limit exposures to the exposure range characterized in the safety and efficacy trials. Also taken into consideration was the finding that no additional benefit was gained from higher exposures from on an efficacy standpoint based on a dose-response analysis of the primary endpoint of TTAS; in fact, slower peramivir clearance in patients with renal impairment will confer a longer time above viral IC_{50} compared to subjects with normal renal function. For these reasons, the Clinical Pharmacology Review Team recommends a reduced dose of peramivir IV 200 mg and 100 mg for patients with creatinine clearance 30-<50 mL/min and <30 mL/min, respectively.

The Review Team concurs with the Applicant that a dose reduction was unnecessary for patients with CL_{CR} of 50 mL/min or greater because of the relatively minor increases in observed exposures in the renal impairment study as well as estimated exposures in population PK simulations.

Due to logistical constraints on PK sampling times in subjects undergoing hemodialysis, accurate systemic exposures (AUC) could not be estimated; however, available data indicate that hemodialysis removes peramivir from systemic circulation, so peramivir should be administeredat a dose selected based on CL_{CR} after hemodialysis in subjects with ESRD in order to more closely match AUC in patients with normal renal function following a dose of 600 mg. If a patient is unable to defer peramivir administration until after hemodialysis, a substantial portion of the dose (80% if a patient undergoes hemodialysis 2 h after peramivir administration, BCX1812-105) will be lost to hemodialysis; therefore, overall systemic exposures will be lower than those expected in patients with normal renal function following a 600 mg dose. However, although plasma concentrations may be lower post-dialysis compared to patients with normal renal function at the same time postdose, the time above viral IC_{50} will be substantially longer in these patients compared to patients with normal renal function because the peramivir half-life is significantly prolonged in ESRD patients, regardless of the timing of hemodialysis (Figure 12). Based on this pharmacodynamic endpoint, the Review Team believes that even if a CL_{CR}-adjusted dose of peramivir is administered pre-hemodialysis, an additional dose of peramivir post-hemodialysis is not needed.

Figure 12. Peramivir plasma concentrations in subjects with normal renal function following a dose of peramivir IV 600 mg (squares) or subjects with ESRD following 2 mg/kg peramivir IV administered 2 h before hemodialysis (open circles) or immediately following hemodialysis (closed circles) compared to median viral IC_{50} values from 0722T0621(dotted line at 1.2 ng/mL, susceptible to NAI) and H1N1 H275Y (dashed line at 51 ng/mL, resistant to NAI) (source: Reviewer's analysis of BCX1812-105 and BCX1812-108 data)



2.3.2.6 Hepatic impairment

The effect of hepatic impairment on peramivir PK was not evaluated. Hepatic impairment is not expected to influence peramivir PK due to the characterization of peramivir clearance as predominantly renal.

2.3.2.7 What pregnancy and lactation use information is there in the application?

No data on peramivir use in pregnant or lactating women is provided in the application. While such data do exist, they are limited to postmarketing reports from Japan as peramivir has not been evaluated in pregnant or lactating women in an adequate well-controlled study.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response, and what is the impact of any differences in exposure on response?

Influenza is a respiratory illness; therefore, it is unsurprising that smoking has been identified as a risk factor for infection with influenza (Horvath KM et al. Am J Respir Cell Mol Biol 2011) and for more severe illness (i.e. hospitalization, Ward et al. Emerg Infect Dis 2011). Smoking status was used as a randomization factor during clinical studies of peramivir efficacy because of its anticipated impact on response. Smoking status was also a covariate in analyses of efficacy, but analyses of the effect of smoking status on response were not performed.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No, there is not an in vitro basis to suspect in vivo drug-drug interactions.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

In human hepatic S9 fractions, peramivir was not extensively metabolized (the only detectable metabolite, an oxidation product, accounted for approximately 4% of peramivir-related material); therefore, peramivir does not appear to be a substrate of CYP enzymes (Study DM98357). The Applicant reported that no metabolites were detected in plasma or urine following administration of peramivir IV to healthy subjects in two non-IND studies (0712T0611 and S-021812-PR-062-C).

2.4.2.3 Is the drug an inhibitor and/or inducer of CYP enzymes?

Peramivir (at concentrations up to 100 uM) did not significantly inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 activity in human liver microsomes (Study DM98399). Peramivir (at concentrations up to 10 ug/mL) did not significantly induce CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 activity in primary cultures of human hepatocytes (Study DM99339).

2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes? Are there other metabolic/transporter pathways that may be important?

Peramivir (at concentrations up to 300 uM) did not exhibit significant directional transport across Caco-2 monolayers, suggesting that peramivir is not a P-gp substrate (Study 7SHIOP2). Peramivir (at 300 uM) did not inhibit digoxin efflux from Caco-2 cells, indicating that peramivir is not a P-gp inhibitor (Study 7SHIOP2).

Characterization of the relationship between CL_{CR} and peramivir CL in the renal impairment study BCX1812-105 demonstrated that peramivir is predominantly eliminated by glomerular filtration; transporters that participate in active tubular secretion or reabsorption are not likely to substantially influence peramivir elimination. This finding is substantiated by the lack of change in peramivir PK following coadministration of the OAT1 and OAT3 inhibitor probenecid (BCX1812-111).

2.4.2.5 Does the label specify coadministration of another drug and if so, has the interaction potential between these drugs been evaluated?

Not applicable – the label does not specify coadministration of another drug.

2.4.2.6 What other comedications are likely to be administered to the target population?

Concurrent use of drugs in the adamantane (e.g. rimantadine, amantadine) or NAI (e.g. oseltamivir, zanamivir) classes of influenza antivirals may be expected with peramivir IV. Concurrent use of paracetamol (acetaminophen), acetylsalicylic acid (aspirin), or other medications to treat cough or cold may also be expected to treat the symptoms of acute influenza.

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are coadministered?

Drug-drug interaction studies were conducted to assess the potential for a PK interaction between peramivir IV and the potential concomitant medications rimantadine (an adamantane), oseltamivir (an NAI), and the oral contraceptive levonorgestrel/ethinyl estradiol (LEVORA®). A drug-drug interaction study was also conducted with peramivir IV and the renal organic anion transporter (OAT) inhibitor probenecid in order to evaluate the potential for a mechanistic PK interaction based on the Applicant's clinical pharmacology knowledge of peramivir. The results of these studies are listed in Table 9. No clinically meaningful PK interactions were observed.

Table 10. Summary of changes in PK parameters in drug-drug interaction studies (source: BCX1812-108, BCX1812-109, BCX1812-110, and BCX1812-111 CSRs)

	Peramivir			Concomitant Drug		
	C_{max} (ng/mL)	AUC_{24h} (ng h/mL)	AUC_{inf} (ng.h/mL)	C_{max} (ng/mL)	AUC_{24h} (ng.h/mL)	AUC_{inf} (ng.h/mL)
BCX1812-108: Single dose three-way crossover study of peramivir IV 600 mg and rimantadine 100 mg PO						
n	21	21	21	21	21	21
GMR (90% CI)	101 (96.3-105)	96.7 (93.8-99.6)	96.8 (93.9-99.7)	106 (100-112)	103 (100-107)	106 (101-111)
BCX1812-109: Single dose three-way crossover study of peramivir IV 600 mg and oseltamivir 75 mg PO						
n	21	21	21	21	21	21

GMR (90% CI)	104 (100-108)	101 (98.8-104)	101 (98.8-104)	120 (100-144)[1] 101 (96.7-106)[2]	102 (96.9-107)[1] 100 (97.4-103)[2]	102 (97.4-107)[1] 101 (98.8-103)[2]
BCX1812-110: Effect of a single dose of peramivir IV 600 mg on levonorgestrel/ethinyl estradiol 0.15/0.03 mg PO						
n	28	28	-	28	28	28
GMR (90% CI)	103 (92.2-116)[3]	104 (99.7-109)[3]	not calculated	93.4 (85.8-102)[4] 100 (91.8-109)[5]	98.1 (90.5-106)[4] 106 (99.4-112)[5]	not calculated
BCX1812-111: Effect of a single dose of probenecid 1 g PO on a single dose of peramivir IM 300 mg						
n	15	-	15	-	-	-
GMR (90% CI)	105 (97.6-112)	not calculated	105 (101-109)	not calculated	not calculated	not calculated

[1] Oseltamivir; [2] [redacted] (b) (4) [3] Historical comparison (BCX1812-108) using a linear mixed-effect model; Ethinyl estradiol; Levonorgestrel

An in vitro study was performed to evaluate the potential for peramivir to inhibit glucuronidation of acetaminophen (DM99401); the results indicated that there was no inhibition of acetaminophen glucuronidation at concentrations of peramivir up to 10 mM (3.8 mg/mL).

2.4.2.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for pharmacodynamic drug-drug interactions. All influenza NAIs (including peramivir) target the viral neuraminidase protein, but the potential for a pharmacodynamic interaction between the NAIs has not been evaluated.

2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Please refer to Section 2.2.4.4 of this review.

2.5 General Biopharmaceutics

2.5.1 Based on the Biopharmaceutics classification system (BCS) principles, in which class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not applicable.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation was used in the pivotal efficacy study 0722T0621 and the supportive study 0815T0631; however, in the supportive study BCX1812-212, peramivir IM was used. In addition, studies in which peramivir IM was used are included in the safety evaluation

of peramivir. Therefore, the relative bioavailability of the IM and IV formulations was evaluated in order to bridge formulations for the clinical safety assessment.

Study BCX1812-113 was a randomized crossover study in which the pharmacokinetics of a single 600 mg dose of peramivir IM and IV were compared in healthy subjects. The two formulations provided similar systemic exposures, with an AUC_{inf} GMR (IM:IV) of 100.5%, with 90% CI of 97.7-103.5%. An evaluation of the clinical and bioanalytical sites performed by the Division of Bioequivalence and GLP Compliance in the Office of Scientific Investigations resulted in the recommendation that the data from this study were acceptable for review.

Study BCX1812-111 was a randomized parallel-group study in which the pharmacokinetics of a single dose of 75, 150, or 300 mg peramivir IM and IV were compared in healthy subjects. The results of this study were in concordance with BCX1812-113, with AUC_{inf} GMRs (IM:IV) ranging from 94.9-105.0% and 90% CI within the traditional bioequivalence bounds of 80-125%.

Overall, the IM and IV formulations and routes of administration provided comparable systemic peramivir exposures (AUC). As expected due to the additional distribution step, the mean C_{max} values observed following IM administration were slightly lower (approximately 20%) compared to those observed after IV administration; this minor difference is not expected to have clinically relevant implications.

2.5.3 What data support or do not support a waiver of in vivo BE data?

Not applicable.

2.5.4 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable for an intravenously administered drug.

2.5.5 When would a fed BE study be appropriate, and was one conducted?

Not applicable for an intravenously administered drug.

2.5.6 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Not applicable for an intravenously administered drug.

2.5.7 What other significant unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

Not applicable for an intravenously administered drug.

2.6 ANALYTICAL

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The Applicant validated a quantitative method (BTM-BA 030) for peramivir in human plasma using solid phase extraction and high-performance liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). Calibration curves for peramivir ranged from 2.5 to 50,000 ng/mL (using a low and a high standard curve). Standards, quality control solutions, blank matrix, and study samples were prepared and analyzed according to validated methods. All samples were analyzed within the timeframe supported by long-term stability data. Evaluation of the standard curve and quality control data indicated that the validated assay was precise and accurate. Additional details can be found in the individual study reviews.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites have been selected for analysis as no metabolites have been identified in clinical studies. Peramivir is an active moiety and is predominantly excreted unchanged in the urine: subjects with normal renal function exhibited an f_e range of 76-97% with a mean of 90.4% and a standard deviation of 7.5% after urine collection for seven days post-dose (BCX1812-105).

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (bound plus unbound) peramivir was measured. This is acceptable because plasma protein binding is minimal in human plasma and is independent of concentration (refer to Section 2.2.5.4 of this review).

2.6.4 What bioanalytical methods are used to assess concentrations?

In addition to BTM-BA 030 (refer to Section 2.6.1), a method was validated by the Application (BTM-BA 033) for peramivir in human urine using ultrafiltration and LC-MS/MS. Calibration curves for peramivir ranged from 10 to 50,000 ng/mL. Standards, quality control solutions, blank matrix, and study samples were prepared and analyzed according to validated methods. All samples were analyzed within the timeframe supported by long-term stability data. Evaluation of the standard curve and quality control data indicated that the validated assay was precise and accurate. Additional details can be found in the individual study reviews.

3. LABELING RECOMMENDATIONS

The following section outlines the labeling recommendations made by the Clinical Pharmacology Review Team based on its interpretation of the review issues at the time this review was filed. These recommendations should not be considered finalized as internal labeling discussions and negotiations with the Applicant are ongoing.

In general, the Review Team found the Applicant's proposed labeling to be appropriate from a clinical pharmacology standpoint. The major changes recommended by the Review Team relate to (b) (4)

The Review Team also recommends a statement clarifying that patients with ESRD undergoing

hemodialysis should receive a peramivir dose based on creatinine clearance in addition to the Applicant's recommendation that peramivir be administered after hemodialysis.

4. APPENDICES

4.1 PHARMACOMETRICS REVIEW

The Pharmacometrics Review begins on page 32 of this document.

4.2 IN VIVO STUDY REVIEWS

The in vivo study reviews begin on page 50 of this document.

- BCX1812-111: Relative bioavailability of peramivir IM and IV 75, 150, and 300 mg
- BCX1812-113: Relative bioavailability of peramivir IM and IV 600 mg
- BCX1812-101: Single and multiple ascending dose study of peramivir IV 0.5-5 mg/kg
- BCX1812-102: Multiple ascending dose study of peramivir IV 0.5-8 mg/kg
- BCX1812-103: Single and multiple ascending dose study of peramivir IV 1-8 mg/kg
- BCX1812-104: Safety and PK of peramivir IV in healthy elderly subjects
- BCX1812-105: Safety and PK of peramivir IV in subjects with renal impairment
- BCX1812-108: Drug-drug interaction study of peramivir IV and rimantadine
- BCX1812-109: Drug-drug interaction study of peramivir IV and oseltamivir
- BCX1812-111: Drug-drug interaction study of peramivir IV and ethinyl estradiol/levonorgestrel

4.3 IN VITRO REVIEWS

The in vitro study reviews begin on page 137 of this document.

- DM99305: Peramivir plasma protein binding
- DM99362: Peramivir plasma protein binding and red blood cell partitioning
- DM98357: In vitro metabolism of peramivir in hepatic S9 fractions
- 7SHIOP: Peramivir transport by or inhibition of P-gp
- DM01372: Transport characteristics of peramivir
- DM98399: Peramivir inhibitory potential of CYP isoforms
- DM99339: Peramivir induction potential of CYP isoforms
- DM99401: In vitro interaction study between peramivir and acetaminophen

OFFICE OF CLINICAL PHARMACOLOGY
PHARMACOMETRIC REVIEW: PERAMIVIR IV

NDA	206426
Drug	Peramivir injection
Trade Name	RAPIVAB®
Pharmacometrics and Clinical Pharmacology Reviewer	Leslie Chinn, Ph.D.
Pharmacometrics Team Leader (acting)	Jeffry A. Florian, Ph.D.
Clinical Pharmacology Team Leader	Islam Younis, Ph.D.
Sponsor	BioCryst Pharmaceuticals, Inc.
Submission Type	Original New Drug Application (New Molecular Entity), Standard
Indication	Treatment of acute uncomplicated influenza in patients 18 years and older
Dosage and Administration	600 mg single dose administered by intravenous infusion for a minimum of 15 minutes

TABLE OF CONTENTS

1 SUMMARY OF FINDINGS

1.1 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions:

1.1.1 Is there sufficient evidence to support the Applicant's proposed dose of peramivir IV 600 mg over 300 mg?

1.1.2 Does the population PK analysis support the Applicant's proposed minimum infusion duration of 15 minutes?

1.1.3 Does the population PK analysis support the Applicant's proposed labeling claims regarding the effects of sex, age, race, body weight, and renal function on peramivir dosing?

1.1.1 Is there sufficient evidence to support the Applicant's proposed dose of peramivir IV 600 mg over 300 mg?

Although there was no evidence of a dose-response relationship for the primary clinical endpoint (time to alleviation of systemic influenza symptoms [TTAS]), there is supportive evidence to justify the selection of a 600 mg dose over 300 mg based on percentage of time exceeding viral IC_{50} values.

The Reviewer and Applicant both conducted PK/PD simulations using a population PK model constructed using PK data from healthy subjects and patients – but excluding data from the dedicated renal impairment study. IC_{50} values for the analysis were obtained by randomly sampling of the observed IC_{50} values from the efficacy studies 0722T0621, 0815T0631, and BCX1812-212. The PD endpoint assessed in the Review Team's simulations was the duration of time that plasma concentrations remained above viral IC_{50} after a single dose of peramivir IV. Time above IC_{50} values was calculated using a simulated peramivir PK time course from the population PK model and calculating the time over the dosing interval which peramivir exposures remained elevated over the selected IC_{50} value. This assessment was repeated 10,000 times using IC_{50} values from: i) all studies; and ii) studies which included strains with containing neuraminidase (NAI) resistance mutation(s).

These analyses demonstrated that the 600 mg dose was correlated with a longer time above IC_{50}, with a median time above IC_{50} of 29 and 39 h for the 300 and 600 mg doses, respectively (QBR Table 1). In contrast, less of a difference was observed between the 300 and 600 mg doses when using IC_{50} values sampled from studies with strains containing NAI resistance mutation(s) (BCX1812-212: median time above IC_{50} of 20 and 22 h for the 300 and 600 mg doses, respectively; QBR Table 1).

While the clinical relevance of this PK/PD analysis has not been established, it is plausible that the duration of time above IC_{50} could be associated with antiviral activity in a greater percentage of patients at the 600 mg dose compared to the 300 mg dose, especially during an influenza season in which NAI resistance is minimal (i.e. the circulating influenza strain is susceptible to NAIs).

For additional information about the methods used in modeling and simulation, please refer to Section 4.3 of the Pharmacometric Review. For additional simulation results, please refer to Section 2.2.4.4 of the QBR.

1.1.2 Do population PK predictions support the Applicant's proposed minimum infusion duration of 15 minutes?

Yes – although an infusion duration of 15 minutes was not evaluated in studies 0722T0621, 0815T0621, and BCX1812-212 (studies all evaluated infusion durations of 30 minutes), the Applicant's proposed minimum infusion duration of 15 minutes is supported by independent simulations conducted using a population PK model developed by the Applicant (BCX1812-PPK-1). Predicted peramivir C_{max} values (mean ± SD) for an infusion duration of 15 and 30 minutes were 46,230 ± 10,530 and 43,490 ± 9,793 ng.h/mL, respectively. These predictions are comparable between infusion durations and suggest that only minimal increases in C_{max} would be observed by shortening the infusion duration from 30 minutes to 15 minutes; therefore, an infusion duration of 15 minutes, as proposed by the Applicant, appears to be reasonable.

For additional information about the methods used in modeling and simulation, please refer to Section 4.3 of the Pharmacometric Review.

1.1.3 Does the population PK analysis support the Applicant's proposed labeling claims regarding the effects of sex, age, race, body weight, and renal function on peramivir dosing?

The population PK model supports the standard dose recommendation of peramivir IV 600 mg regardless of sex, age, race, and body weight. However, simulations conducted by the Review Team using a population PK model developed by the Applicant estimate that following a dose of 600 mg, systemic peramivir exposures (AUC) would be higher in patients with moderate (CL_{CR} 30-50 mL/min) or severe (CL_{CR} <30 mL/min) renal impairment. These simulation results are similar to observations from the Applicant's dedicated renal impairment trial that showed increases of 4-fold and 5-fold in subjects with moderate and severe renal impairment, respectively; therefore, the Review Team recommends a dose reduction to 200 and 100 mg in patients with creatinine clearance 30-<50 and <30 mL/min, respectively.

Covariate analysis of sex, age, race, body weight, and renal function

Sex, age, race, and body weight were not identified as clinically relevant covariates during the Applicant's population PK analysis (S-021812-CB-137C). The Applicant evaluated sex, age, race, body weight, and renal function as fixed effects on CL and sex, age, race, and body weight on V_1 (volume of the central compartment). Sex and race (Japanese and US) did not substantially influence peramivir PK; however, renal function had a significant effect on AUC. Please refer to Section 3.1.1 for additional information.

Predicted exposures in patients with renal impairment

A dedicated renal impairment study conducted in otherwise healthy subjects with renal impairment (n=6 subjects per group) showed increases in AUC_{inf} of 28, 302, and 412% in subjects with mild (CL_{CR} 50-80 mL/min), moderate (CL_{CR} 30-49 mL/min), and severe (CL_{CR} <30 mL/min) renal impairment, respectively, compared to subjects with normal renal function following a single administration of peramivir IV 2 mg/kg. If AUC values are adjusted to a fixed

dose of 600 mg, the increases in AUC_{inf} are 42, 307, and 454% in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. The extent of increase in peramivir AUC in the moderate renal impairment group is slightly higher than would be expected based on the correlation between renal function and peramivir clearance. This may be explained by the renal function distribution in the moderate renal impairment group: when renal function is assessed by eGFR using the MDRD equation (instead of estimating CL_{CR} using Cockcroft-Gault), the median is 30.8 mL/min/1.73m^2 and three of the six subjects in the group fall below the GFR cutoff of 30 mL/min/1.73 m^2 for severe renal impairment.

The observed increases in overall systemic exposures were driven by slower clearance with increasing renal dysfunction (median half-life was 23.7, 28.7, and 30.7 h in subjects with mild, moderate, and severe renal impairment, respectively, compared to 20.7 h in subjects with normal renal function). Evaluation of the relationship between peramivir clearance and creatinine clearance suggested that peramivir is primarily eliminated through glomerular filtration (for additional information, please refer to the review of Study BCX1812-105).

The Applicant incorporated these data (in addition to Phase 1 PK data and PK data from the pivotal efficacy study 0722T0621) into a population PK model in which there was a single route of peramivir elimination, which was dependent on creatinine clearance (S-021812-CB-137-C). The Review Team performed independent simulations using this model to estimate peramivir exposures in 10,000 patients with demographic characteristics randomly sampled from the efficacy studies (0722T0621, 0815T0631, and BCX1812-212) and a uniform distribution of creatinine clearance. The model predicted overall systemic exposures that were in concordance with the findings of the renal impairment trial and the inherent PK variability within renal function groups (e.g. due to non-uniform distribution of creatinine clearance), with simulated increases in median AUC of 35, 280, and 642% for patients with mild, moderate, and severe renal impairment, respectively, compared to patients with normal renal function.

The model was subsequently used to estimate peramivir AUC at various doses for patients with renal impairment (Table 2, Figure 1).

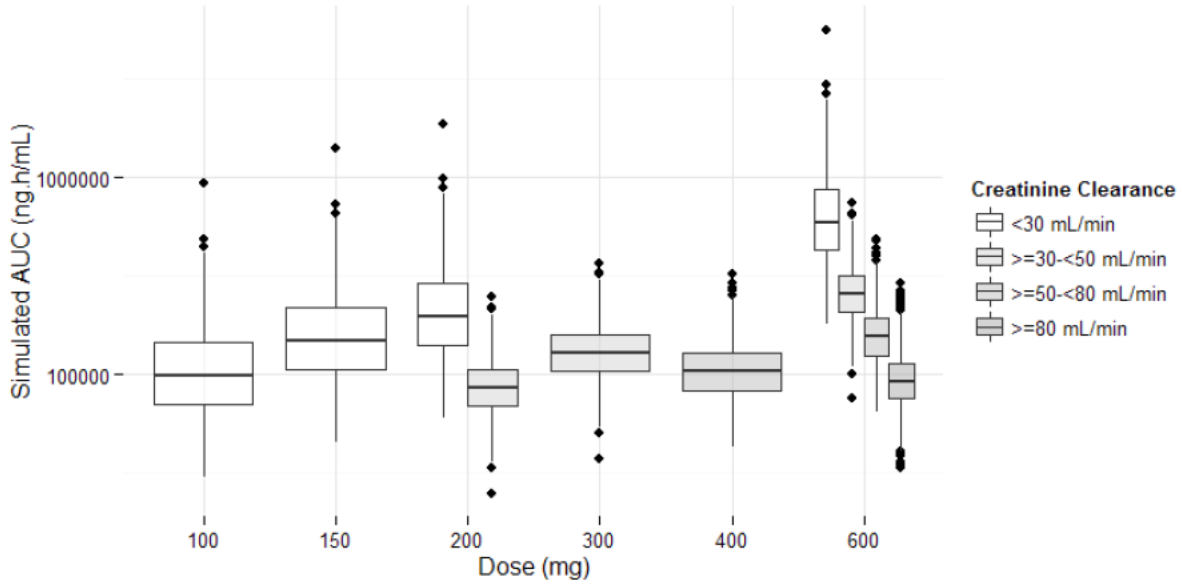
Table 1. Observed and predicted peramivir median AUC values following a single IV administration[a]

Source	Population	Dose (mg)	Median AUC (ng.h/mL)	IQR (ng.h/mL)
Observed	0722T0621 [pivotal efficacy trial	600	78,720	73,650-84,880
	BCX1812-106 [TQT study]	600	97,920	86,200-107,400
		1200	196,200	181,100-199,700
Observed	BCX1812-105 Normal renal function (CL_{CR} ≥80 mL/min)	2 mg/kg[b]	92,520	88,560-97,790
	Mild renal impairment (CL_{CR} 50 to <80 mL/min)	2 mg/kg[b]	135,100	116,600-157,000
	Moderate renal impairment	2 mg/kg[b]	373,600	331,800-442,900

	(CL_{CR} 30 to <50 mL/min)			
	Severe renal impairment (CL_{CR} 10 to <30 mL/min)	2 mg/kg[b]	483,500	446,800-649,400
Simulated	Normal renal function (CL_{CR} ≥80 mL/min)	600	92,650	75,373-113,596
	Mild renal impairment (CL_{CR} 50 to <80 mL/min)	600	124,937	156,014-194,143
		400	83,291	104,010-129,429
	Moderate renal impairment (CL_{CR} 30 to <50 mL/min)	600	259,202	207,134-320,564
		300	129,601	103,567-160,282
		200	86,401	69,045-106,855
	Severe renal impairment (CL_{CR} 10 to <30 mL/min)	600	594,796	426,273-879,192
		200	198,265	142,091-293,064
		150	148,699	106,568-219,798
		100	99,133	71,045-146,532

[a] The Applicant's categorization of renal function based on creatinine clearance was used
[b] Normalized to 600 mg

Figure 1. Observed and predicted peramivir AUC following a single IV administration



The Review Team concurred with the Applicant that a dose reduction was unnecessary for patients with CL_{CR} of 50 mL/min or greater because of the relatively minor increases in observed exposures in the renal impairment study as well as estimated exposures in population PK simulations.

During the dose evaluation process for patients with moderate and severe renal impairment, the primary aim of the Review Team was to match exposures associated with a single 600 mg

administration of peramivir IV to subjects with normal renal function (0722T0621 600 mg arm, BCX1812-106 600 mg arm), with an upper exposure limit defined by a single 1200 mg administration of peramivir IV to subjects with normal renal function (BCX1812-106 1200 mg arm). These criteria were best met by a dose of 200 mg for patients with creatinine clearance 30-<50 mL/min and a dose of 100 mg for patients with creatinine clearance less than 30 mL/min. PK/PD simulations indicate that the median time above viral IC_{50} will be longer for patients with renal impairment, even at these reduced doses (median time above IC_{50} values of 35, 54, 61, and 80 h for subjects with normal renal function and patients with mild, moderate, and severe renal impairment, respectively). These estimates are consistent with the observed increases in terminal elimination half-life that were correlated with decreasing renal function in the renal impairment study.

Because of the dosage "increment" (peramivir injection is supplied in 200 mg vials), consideration was also given to the 200 mg dose for patients with severe renal impairment. This dose is expected to result in exposures that are substantially higher than those observed following a 600 mg dose to patients with normal renal function in a subset of patients (see Table 2 and Figure 1) and is not expected to provide an improvement in terms of efficacy over the 100 mg dose based on the primary efficacy endpoint. Therefore, although administration may be more inconvenient due to the dosage increment, the Reviewer concludes that a dose of 100 mg for patients with creatinine clearance less than 30 mL/min is appropriate based on exposure-matching in a patient population in which safety data are limited (i.e. patients with severe renal impairment).

Although peramivir PK parameters were not calculated for patients with ESRD due to PK sampling limitations, available data showed decreases in AUC_{inf} of approximately 80% following hemodialysis; therefore, peramivir IV should be administered after hemodialysis for patients with ESRD following the dose recommendations for creatinine clearance classification, although the dose.

1.2 RECOMMENDATIONS

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed this Application and recommends approval of a single dose of peramivir 600 mg administered intravenously over a minimum of 15 minutes for the treatment of uncomplicated influenza in adults 18 years and older. The Reviewer agrees with the Sponsor's conclusions that no dose adjustments based on age, sex, race, or body weight are necessary based on population PK analyses. However, based on population PK and PK/PD analyses, the Reviewer recommends a dose reduction to 200 mg and 100 mg (administered over a minimum of 15 minutes) in patients with creatinine clearance 30-<50 mL/min and less than 30 mL/min, respectively.

2 PERTINENT REGULATORY BACKGROUND

Peramivir is a novel inhibitor of influenza neuraminidase (NAI). Two NAIs are currently approved for the treatment of acute uncomplicated influenza in adults in the US: oseltamivir (Tamiflu®) and zanamivir (Relenza®). Because peramivir is administered via IV infusion, it will serve as a treatment option for patients who are unable to swallow or inhale medications due to illness or for other reasons, as oseltamivir is administered orally and zanamivir is administered by nasal inhalation. Because NAIs prevent the release of new viral particles from infected host

cells, administration early in the disease course is considered crucial in order to have a clinically meaningful effect. Therefore, peramivir should be administered within 48 h of the appearance of influenza signs and symptoms.

The peramivir development program includes a number of studies evaluating two different formulations of peramivir (IV and IM) as well as the efficacy of peramivir for two separate indications (uncomplicated influenza and complicated influenza in a hospital setting). (b) (4) and continued to pursue an indication for uncomplicated influenza.

The current Application is based on efficacy data from the pivotal Phase 2 trial 0722T0621 (a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single administration of peramivir IV 300 and 600 mg, n=298) as well as pooled safety data from this and other trials, including trials conducted using the peramivir IM formulation. Data from two supportive Phase 2 trials BCX1812-212 (a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of a single administration of peramivir IM 600 mg) and 0815T0631 (a randomized, double-blind, active-controlled trial evaluating the safety and efficacy of a single administration of peramivir IV 300 and 600 mg in comparison to oseltamivir 75 mg BID PO for five days) were also evaluated. These three studies contributed pharmacodynamic data (i.e. viral IC_{50} values) that allowed exploration of the peramivir PK/PD relationship during the Clinical Pharmacology Review Team's evaluation of the Applicant's selected dose.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 POPULATION PK ANALYSIS

3.1.1 Renal impairment model

Objectives

- Evaluate the influence of factors including age, body weight, gender, and renal function on peramivir PK
- Compare the PK of peramivir between US and Japanese subjects
- Compare the PK of peramivir between uninfected subjects and influenza patients

Studies included in the analysis

- **Hi-06-103**: Phase 1 single and multiple dose study in healthy subjects
- **Hi-06-104**: Phase 1 single and multiple dose study in healthy elderly
- **Hi-06-105**: Phase 1 single dose study of peramivir IV 2 mg/kg in subjects with renal impairment
- **0712T0611**: Phase 1 multiple dose study in healthy Japanese subjects
- **0714T0612**: Phase 1 high dose study in healthy Japanese subjects
- **0722T0621**: Phase 2 placebo-controlled efficacy and safety study of a single dose of peramivir IV 300 or 600 mg to adult Asian patients with uncomplicated influenza

A summary of the demographic information for subjects used in the analysis is listed in Table 3.

Table 2. Summary of demographic information (source: S-021812-CB-137-C Table 1)

Number of subjects (Samples)			Age (year)	Height (cm)	BWT (kg)	BMI (kg/m^2)	Scr (mg/dL)	CLcr* (mL/min)
Japanese Patients		Mean	34	164.2	62.2	23.0	0.77	112
		SD	10	9.1	14.0	4.2	0.18	24
Total	198 (558)	Minimum	20	143.0	39.2	16.1	0.42	61
Male	101 (288)	Median	32	164.3	60.0	22.3	0.75	109
Female	97 (270)	Maximum	62	188.5	109.8	44.8	1.25	195
Healthy Japanese		Mean	24	172.7	64.4	21.6	0.73	144
		SD	4	4.8	5.9	1.7	0.10	21
Total	36 (1092)	Minimum	20	163.4	53.3	18.6	0.60	101
Male	36 (1092)	Median	23	173.4	64.2	21.4	0.72	141
Female	0 (0)	Maximum	39	182.0	76.8	24.6	0.98	188
US Subjects		Mean	47	170.7	78.6	26.9	1.7	92.8
		SD	19	9.9	13.5	3.8	2.1	42.3
Total	98 (1549)	Minimum	19	150.0	50.0	18.0	0.6	7.2
Male	57 (859)	Median	46	172.0	78.6	26.8	1.0	98.5
Female	41 (690)	Maximum	79	189.0	113.0	37.0	10.9	180.6
All Subjects		Mean	37	167.0	67.3	24.0	1.03	109.6
		SD	15	9.6	15.1	4.3	1.23	33.6
Total	332 (3199)	Minimum	19	143.0	39.2	16.1	0.42	7.2
Male	194 (2239)	Median	32	167.9	65.1	23.4	0.80	111.3
Female	138 (960)	Maximum	79	189.0	113.0	44.8	10.9	195

Mean, SD: Arithmetic mean and standard deviation.
*: CLcr was calculated by Cockcroft-Gault formula.

Model selection

Based on previous investigations, the Applicant assumed that a three-compartment model would best describe peramivir PK. The basic PK parameters were total body clearance (CL), intercompartment clearance (Q_1, Q_2) and the distribution volume of central (V_1) and peripheral compartments (V_2, V_3). The interindividual variability for the PK parameters was assumed to follow a log-normal distribution described by an exponential error model.

The Applicant used a traditional forward addition (p-value cutoff of 0.05) backward elimination (p-value cutoff 0.01) to construct a covariate model in which age, gender, body weight, and CL_{CR} were tested as covariates on CL and age, gender, and body weight were tested as covariates on V_1. A linear model was used for the continuous variables age, body weight, and CL_{CR}, an additive model was used for gender, and a proportional model was used for influenza infection. A three-compartment model with body weight and age as predictors of V_1 and creatinine clearance (up to 115 mL/min) and age as a predictor of CL was selected as the final model. The parameters of the final model and associated interindividual variability are listed in Table 6. Influenza infection was associated with a higher (18%) CL and lower (5%) V_1 compared to uninfected subjects.

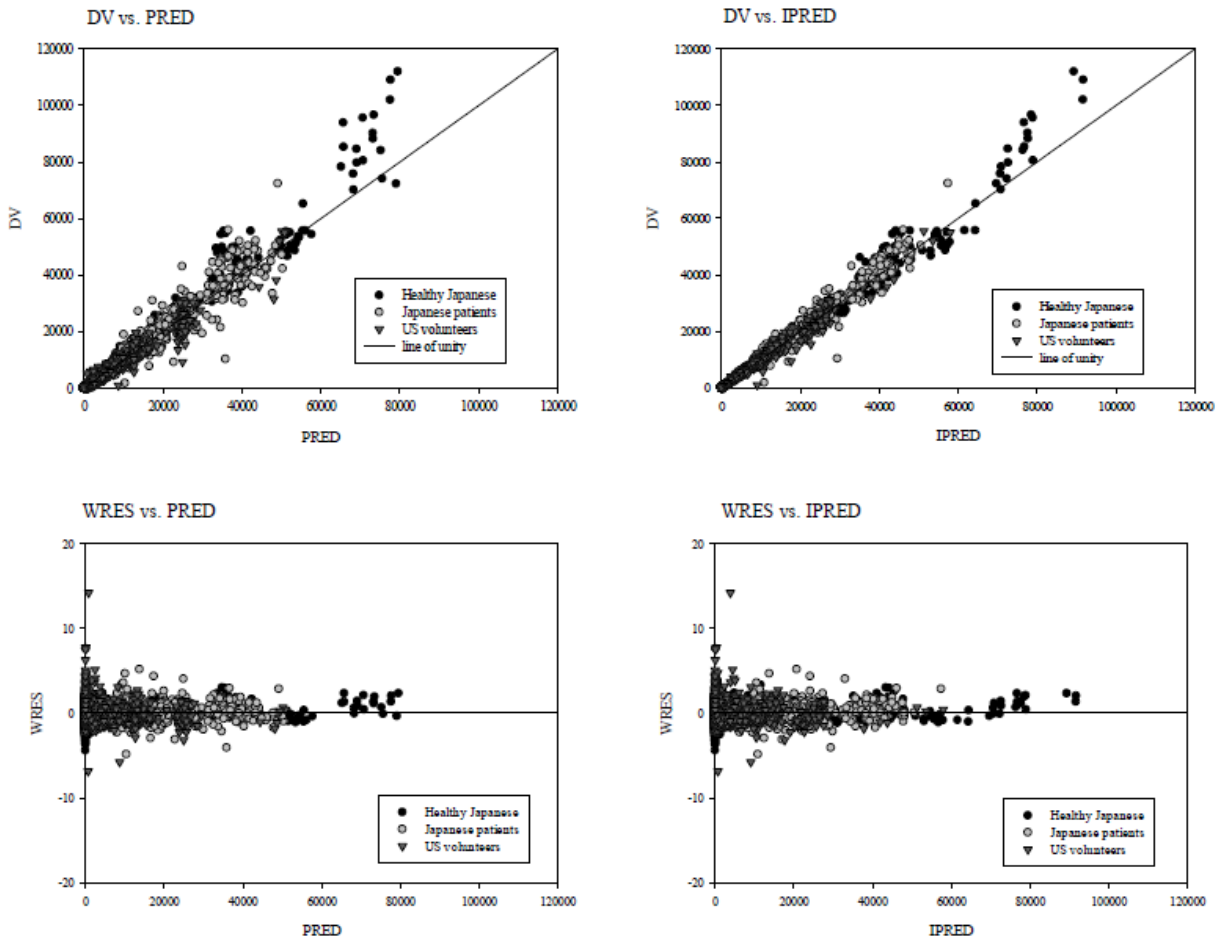
Table 3. Summary of final model (Model 36) parameters (source: S-021812-CB-137-C Table 5)

Parameter	Population Mean	Inter-individual Variability (CV)
CL (L/hr)	CLcr<115 (6.70×CLcr/109.6 - 0.222×Age/37)×(1+0.182×PID) CLcr≥115 (6.70×115/109.6 - 0.222×Age/37)×(1+0.182×PID)	18.0%
Q_1 (L/hr)	6.29	-
Q_2 (L/hr)	0.121	15.7%
V_1 (L)	(0.535+9.13×BWT/67.3)×(1-0.0542×PID)	17.3%
V_2 (L)	6.00	14.5%
V_3 (L)	3.44	18.1%
σ_1 (Exponential error for intra-individual variability)		12.6%
σ_2 (additive error for intra-individual variability)		0.511 ng/mL

The model was constructed based on all data of Phase 1 studies in Japan and USA and Phase 2 study in Japan.
CLcr: creatinine clearance (mL/min), Age: age (years old), BWT: body weight (kg),
PID: 0 for uninfected subjects in Phase 1, 1 for influenza patients
Doses in Phase 2 study in Japan were corrected as estimated actual doses by multiplying 0.885.
-: Not estimated

The goodness-of-fit plots for the fitted concentrations and the weighted residuals from this model are provided in Figure 2. In general, no significant biases were observed in the fit of the data across the range of concentrations fitted over time and the model was expected to provide reasonable estimates of peramivir plasma concentrations when used for PK simulations.

Figure 2. Basic goodness-of-fit plots for final model (source: S-021812-CB-137-C Figure 8)



Simulations (5000 subjects with uniform distributions of CL_{CR}, age [mean ± SD 34 ± 10 years], and body weight [mean ± SD 62.2 ± 14.0 kg]) were performed using the final model to investigate the effect of CL_{CR}, age, and body weight on peramivir PK. The results are discussed in Section 1.1.3 and displayed in Table 1 of this review. Because renal function had a profound effect on AUC, the effect of age and body weight on systemic peramivir exposures were predicted in the context of varying degrees of renal insufficiency. Predicted median AUC values increased slightly with age but was unaffected by body weight, and predicted median C_{max} values increased with lower body weight (as expected based on the correlation between volume and C_{max}) but was unaffected by age; no dose adjustments are recommended by age or body weight.

Applicant's conclusions

The Applicant constructed a three-compartment model to describe the pharmacokinetics of peramivir. Renal function (CL_{CR}) was the most significant covariate on peramivir clearance; the relationship between peramivir total and renal clearance and creatinine clearance was informed by data from the renal impairment study (BCX1812-105). Age was a covariate on CL and body weight was a covariate on V_1. No PK differences were found between genders or between US and Japanese subjects. There were minor differences between peramivir PK in infected patients compared to healthy subjects (CL 18% higher and V_1 5% lower in patients compared to healthy

subjects); the physiological basis for these differences is unknown and they are unlikely to be clinically meaningful.

AUC was found to be highly dependent on CL_{CR} and independent of body weight, while C_{max} was influenced by body weight and independent of age and renal function. Simulations performed by the Applicant for daily peramivir administration (b) (4) in subjects with moderate and severe renal impairment suggested that dose reductions of 1/3 and 1/6 would provide similar systemic exposures to subjects with normal renal function (please refer to the review of BCX1812-105 for additional details).

3.1.2 PK/PD Analysis

Objectives

- Define the population PK of peramivir IV and IM
- Define the relationship between dose and likely metrics of efficacy, such as time above viral IC_{50}
- Test specific hypotheses including the effect of race on the PK of peramivir, independent of body weight and other covariates

Population PK model

Studies included in the analysis

- **0712T0611**: Phase 1 placebo-controlled PK and safety study of single and multiple doses of peramivir IV 100, 200, and 400 mg QD and 400 mg BID for five days to healthy Asian adult males (24 subjects, 816 PK observations)
- **0714T0612**: Phase 1 placebo-controlled PK and safety study of single and multiple doses of peramivir IV 800 mg QD for six days to healthy Asian adult males (12 subjects, 276 PK observations)
- **0722T0621**: Phase 2 placebo-controlled efficacy and safety study of a single dose of peramivir IV 300 or 600 mg to adult Asian patients with uncomplicated influenza (198 subjects, 559 PK observations)
- **0815T0631**: Phase 3 active-controlled efficacy and safety study of a single dose of peramivir IM 300 or 600 mg to adult Asian patients with uncomplicated influenza (728 subjects, 2102 PK observations)
- **BCX1812-113**: Relative BA study comparing peramivir IV 600 mg to peramivir IM 600 mg in healthy adult subjects (24 subjects, 797 PK observations)
- **BCX1812-212**: Phase 2 placebo-controlled efficacy and safety study of a single dose of peramivir IM to adult patients with uncomplicated influenza (196 subjects, 383 PK observations)
- **BCX1812-311**: Phase 2 placebo-controlled efficacy and safety study of a single dose of peramivir IM 300 mg to adult patients with uncomplicated influenza (57 subjects, 108 PK observations)

A summary of the demographic information for subjects used in the analysis is listed in Table 3.

Table 4. Summary of demographic information (source: BCX1812-PPK-1 Table 1)

Study	0712T0611	0714T0612	0722T0621	0815T0631	BCX1812-113	BCX1812-212	BCX1812-311
N	24	12	198	728	24	196	58
Weight (kg) mean (SD)	64.2 (6.2)	65.1 (5.6)	62.2 (14)	62.1 (13)	75.4 (13)	78 (19.5)	84.8 (20.5)
Age (years) mean (SD)	24.6 (4.2)	25.5 (4.6)	34.8 (10.2)	35.9 (11.8)	42.5 (12.7)	34.9 (12.1)	33.1 (12.6)
Gender (% male)	100	100	51	52	54	50	51
Race (% Asian)	100	100	100	100	0	7.7	3.5
CRCL[a] (mL/min*) mean (SD)	143.9 (20.2)	141.7 (21.9)	111.1 (23.9)	100.5 (25.1)	111.2 (20.4)	116.6 (37.5)	122.6 (37.3)

[a]Calculated by Cockcroft-Gault[V1]

Model selection

The Applicant used a traditional forward addition (p-value cutoff of 0.05) backward elimination (p-value cutoff 0.01), along with an inspection of diagnostic figures and consideration of biological plausibility, was used to develop the population PK model. The initial model was a simple one-compartment model with no covariates which consistently underpredicted observed concentrations, suggesting the presence of a peripheral compartment. A two-compartment model with body weight and race as predictors of volume and creatinine clearance (up to 100 mL/min) as a predictor of k_e was selected as the final model. The parameters of the final model are listed in Table 4 and the between-subject variance terms are listed in Table 5.

Table 5. Summary of final model (Model 30) parameters (source: BCX1812-POPPK-1 Table 4)

Parameter	Estimate	Standard Error of the Estimate
THETA[a](1) Central Volume of distribution (liters)	12.56	NA[b]
THETA(2) Ke, Elimination rate constant (/hr)	0.2530	NA
THETA(3) Additive residual error term (ng/mL)	2.495	NA
THETA(4) Proportional residual error term	0.235	NA
THETA(5) Absorption rate constant (/hr) for IM dose	10.37	NA
THETA(6) K23 (/hr)	8.716E-03	NA
THETA(7) K32 (/hr)	0.0529	NA
THETA(8) Effect of weight on V (power model)	0.5623	NA
THETA(9) Effect of creatinine clearance on Ke (linear additive)	2.469E-03	NA
THETA(10) Effect of race on Volume (proportional)	-7.680E-03[c]	NA
THETA(11) Effect of gender on V (Fixed to zero)	0 (FIXED)	NA

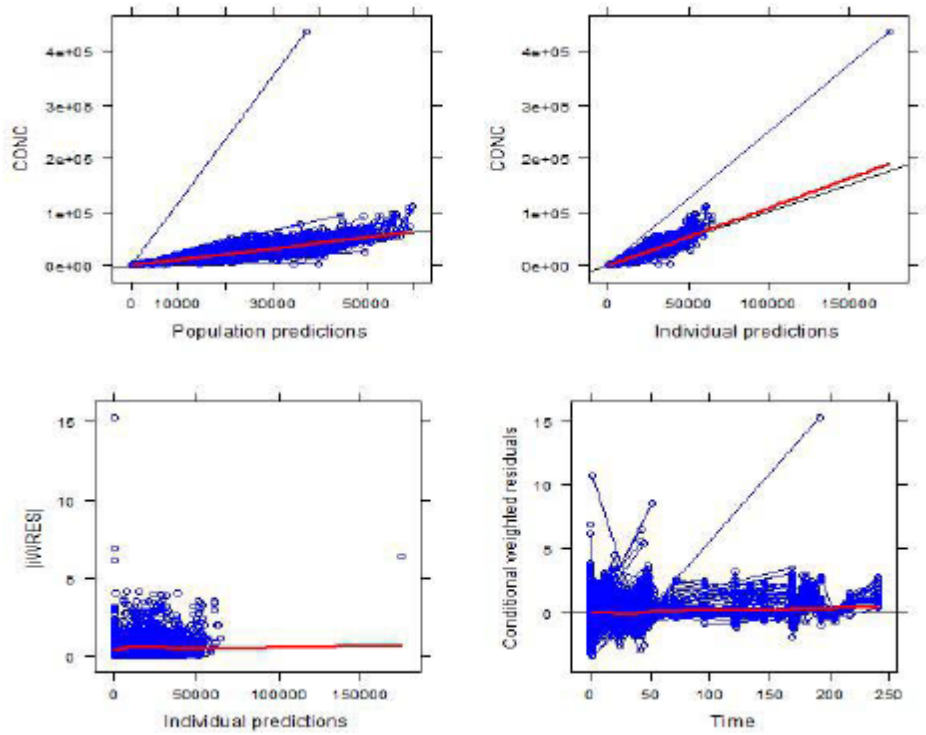
[a]THETAs are the fixed effect parameters, e.g., volume, Ke, Ka
[b] NA Not available, as the final model did not complete a covariance step
[c] a negative value suggests that the volume is decreased, proportionally, by 0.8% (1-exp(-0.00768)

Table 6. Between-subject variance terms for the final model (source: BCX1812-POPPK-1 Table 5)

	OMEGA(1,n)	OMEGA(2,n)	OMEGA(3,n)	OMEGA(4,n)
OMEGA(n,1)	3.217301E-02			
OMEGA(n,2)	4.084722E-02	0.1942859		
OMEGA(n,3)	-1.643424E-02	-2.090357E-02	3.688516E-02	
OMEGA(n,4)				9.554344E-03

The goodness-of-fit plots for the fitted concentrations and the weighted residuals from this model are provided in Figure 2. In general, no significant biases were observed in the fit of the data across the range of concentrations fitted over time and the model was expected to provide reasonable estimates of peramivir plasma concentrations when used for PK/PD analyses.

Figure 3. Basic goodness-of-fit plots for final model (source: BCX1812-POPPK-1 Figure 28)



PD model

Studies included in the analysis

- **0722T0621** (198 subjects, 252 PD observations)
- **0815T0631** (728 subjects, 706 PD observations)
- **BCX1812-212** (196 subjects, 259 PD observations)

A summary of the virology information is listed in Table 4.

Table 7. Summary of virology information (source: BCX1812-PPK-1 Table 2)

Study	0722T0621	0815T0631	BCX1812-212
Peramivir IC_{50} (ng/mL) geometric mean, CV%	0.440 (44)	2.13 (312)	10.1 (195)
Baseline Viral load ($log_{10}TCID_{50}$) mean, SD	4.17 (1.55)	4.26 (1.91)	2.43 (1.67)
N	252	706	259
% with any Influenza type A	98.7	91.3	75.6
% with any Influenza A/H1N1	72.5	54.5	65.9
% with Influenza A/H1N1/H275Y	0.0	44.8[a]	61.8

[a]This was based on 81% of type A(H1 subtype), a mixture of A(H1 subtype) and A(H3 subtype) and two A(subtype (H3) being found to have the H274Y substitution.

PK/PD simulations

The Applicant used the Markov Chain Monte Carlo method to select a Gompertz hazard model with a simple E_{max} relationship between time above IC_{50} and hazard of recovery (alleviation of systemic influenza symptoms). The final model predicted that the "risk" of alleviation of symptoms increases quickly when plasma concentrations initially achieve IC_{50}, but the risk plateaus with longer duration above IC_{50}, which appeared to be consistent with the mechanism of NAI activity as well as the course of influenza. The ET_{50} (time above IC_{50} that results in 50% of maximum effect) was 21.8 h; the Applicant selected a PD endpoint of plasma concentrations above IC_{50} for 43.6 h, which is expected to result in 75% of the maximum possible effect of peramivir on the recovery hazard and was considered to be a reasonable clinical duration given the typical duration of illness.

The Applicant used the population PK model described above (two-compartment with effects of race and body weight on volume and creatinine clearance on elimination) to perform simulations in 1000 patients following a single dose of peramivir IV 300 or 600 mg infused over 15 minutes, then used simulated plasma concentrations to calculate the percent of patients with plasma concentrations above IC_{50} for 43.6 h. The Applicant's simulations showed that in a "typical" influenza season (e.g 0722T0621), the 300 and 600 mg doses of peramivir IV perform similarly, with 93 and 98% of patients achieving the PD endpoint. However, in a "low susceptibility" influenza season (when the circulating strain confers NAI resistance, e.g. BCX1812-212), the 600 mg dose provided additional value compared to the 300 mg dose (12.7 and 21.1% of patients reaching the PD endpoint for the 300 and 600 mg doses, respectively). The Applicant's simulations are displayed in Table 7.

Table 8. Fraction of simulated population with plasma concentrations above IC_{50} for at least 43.6 h (source: BCX1812-POPPK-1 Table 9)

Dose	IC_{50} from all studies	IC_{50} from only study BCX1812-212	IC_{50} from only study 0722T0621
300 mg IV over 15 minutes	43.9%	12.7%	93.2%
600 mg IV over 15 minutes	52.1%	21.1%	98.4%

Applicant's conclusions
The Applicant constructed a two-compartment model to describe the pharmacokinetics of peramivir. The elimination rate constant was dependent on CL_{CR} up to 100 mL/min. Body weight and Asian race were covariates on volume. The effect of Asian race on weight-adjusted volume of distribution was small (<2%) and is unlikely to be clinically meaningful.

The Applicant based the selection of time above viral IC_{50} as the driver of pharmacodynamic response on peramivir mechanism of action and basic anti-infective principles and used a standard E_{max} model to explore the relationship between time above IC_{50} and hazard of alleviation of symptoms. (The duration of symptoms prior to treatment was evaluated as a covariate but did not have an effect.) The results of the Applicant's PK/PD simulations suggested that during a "typical" influenza season, the 600 mg dose would permit a higher percentage of patients to achieve a target time (2 x EC_{50}, or 43.6 h) above IC_{50} compared to the 300 mg dose.

4 REVIEWER'S ANALYSIS

4.1 OBJECTIVES

The Reviewer conducted independent analyses for the following objectives:

1. To evaluate the appropriateness of the Applicant's proposed dose of peramivir IV 600 mg over 300 mg
2. To evaluate the effect of reducing the infusion time to 15 minutes, rather than the 30 minute infusion duration specified in 0722T0621
3. To evaluate the adequacy of the Applicant's population PK model to predict the effects of covariates on peramivir pharmacokinetics

4.2 METHODS

4.2.1 Data Sets

Data sets used are summarized in Table 10.

Table 9. Analysis data sets

Study Number	Name	Link to EDR
BCX1812-POPPK-1 Population PK	data.xpt	\\cdsesub1\evsprod\nda206426\0003\m5\datasets\bcx1812-ppk-1\tabulations\legacy\data.xpt
BCX1812-POPPK-1 PK/PD	pddata.xpt	\\cdsesub1\evsprod\nda206426\0003\m5\datasets\bcx1812-ppk-1\tabulations\legacy\pddata.xpt
S-021812-CB-137-C Population PK	[Data sets and ctl files not provided]	\\cdsesub1\evsprod\nda206426\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\s-021812-cb-137-c\s-021812-cb-137-c-study-report.pdf

4.2.2 Software

Modeling and simulations were performed using NONMEM version 7.3. Statistical summarization and plotting were performed using R.

4.2.3 Models

The Applicant's final population PK and PK/PD models were used as a starting point for the Reviewer's analysis.

BCX1812-POPPK-1

The PK model structure for this analysis was a three-compartment model. The Applicant's PD model was not used in the Reviewer's assessment of time above IC_{50} values. The Reviewer performed simulations based on the simulated plasma concentration-time profiles for 10,000 virtual patients with demographic information (including baseline viral IC_{50}) randomly sampled from the efficacy trials 0722T0621, BCX1812-212, and 0815T0631 for each simulation.

S-021812-CB-137-C

The PK model structure for this analysis was a two-compartment model. To evaluate dose reductions for patients with renal impairment, the Reviewer performed simulations based on the simulated plasma concentration-time profiles for 10,000 virtual patients with demographic information randomly sampled from the efficacy trials 0722T0621, BCX1812-212, and 0815T0631 for each simulation. Uniform distributions were simulated for CL_{CR}.

4.3 RESULTS

The Applicant's population PK models were generally found to be acceptable and the identified covariate effects (Asian race and body weight on volume and creatinine clearance on peramivir clearance) were biologically plausible. The Reviewer concurs with the Applicant's assessment that no dose adjustments are needed based on race or body weight (b) (4)

Simulations of peramivir PK in patients with renal impairment using the population PK model constructed in BCX1812-POPPK-1 indicated that this model routinely underpredicted exposures in patients with moderate and severe renal impairment compared to observed data. This phenomenon is likely due to the paucity of PK data from subjects with renal dysfunction used during model construction, which permitted inaccuracy in parameterization of CL.

Therefore, the Reviewer used the population PK model constructed in S-021812-CB-137-C to estimate peramivir exposures in patients with renal impairment, as this model was informed by data from the renal impairment study that characterized peramivir clearance as being highly correlated with creatinine clearance such that active renal and non-renal processes are negligible. The simulated increases in peramivir exposures in patients with moderate (defined as creatinine clearance 30-<50 mL/min) and severe (defined as creatinine clearance <30 mL/min) renal impairment compared to subjects with normal renal function were found to be consistent with the observed increases in the renal impairment study BCX1812-105.

Due to the magnitude of the increases in peramivir exposures in patients with moderate or severe renal dysfunction even in the context of a single dose, (b) (4) the Reviewer recommends reduced doses of 200 mg and 100 mg for patients with creatinine clearance 30-<50 and less than 30 mL/min, respectively, based on

exposure-matching to the recommended dose (600 mg) in patients with normal renal function as well as the limited safety data currently available in patients with renal impairment (see Section 1.1.3 and Section 2.3.2.5 in the QBR). These dose reductions are in line with those recommended for other intravenously-adminstered renally excreted drugs (e.g. doripenem, gabapentin).

5 LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Peramivir_Analyses.R	Functions for data summarization, dose-response analysis, processing of output from PK/PD and population PK simulations, and plotting	Reviews\Ongoing PM Reviews\Peramivir_NDA206426_LC\ER Analyses
run5.mod, run5.lst, sdtab5, patab5, cotab5, catab5	Reviewer's final population PK model and output files	Reviews\Ongoing PM Reviews\Peramivir_NDA206426_LC\PPK Analyses

Trial BCX1812-111
A Phase 1, Open Label, Single-Dose, Single-Center, Treatment Sequence-Randomized, Parallel-Group Study to Evaluate the Pharmacokinetics, Bioavailability, and Safety of Intramuscular Peramivir Administered to Healthy Subjects

Trial Period
8 Sept to 30 Oct 2006
Final report date: 23 Jul 2009

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. The primary goal of this study was to evaluate peramivir pharmacokinetics and bioavailability following administration of peramivir by IV infusion or IM injection(s). Additionally, the effect of coadministration of oral probenecid on peramivir exposure was evaluated to assess involvement of renal organic anion transporters (OATs) in peramivir elimination.

Trial Objectives
The primary objective of the trial was to:

- evaluate the absolute bioavailability of a range of single intramuscular doses of peramivir

The secondary objective of the trial was to:

- evaluate the pharmacokinetic profile and safety of a range of single intramuscular and intravenous doses of peramivir
- evaluate the effect of concomitant administration of probenecid on the pharmacokinetics of a range of single intramuscular doses of peramivir

Trial Design
This was an open-label, single-dose, single-center, treatment sequence-randomized, parallel-group study. There were three treatments and three cohorts:

Treatment A peramivir IV
Treatment B peramivir IM
Treatment C peramivir IM with 1 g oral probenecid

Cohort 1 peramivir 75 mg
Cohort 2 peramivir 150 mg

Cohort 3 peramivir 300 mg

Eligible subjects were allocated to one of three cohorts and randomized within the cohort to one of three treatment sequences: ABC, BCA, or CAB. Treatments were administered on Days 1, 8, and 15 and were separated by a seven day washout period. Subjects were confined to the clinic beginning 24 h prior to dosing until 72 h post-dose. A final evaluation was performed three days after the final 72 h post-dose sample collection (Day 21).

Rationale for Dose Selection

Single doses of peramivir IV 1 to 8 mg/kg were well-tolerated in study BCX1812-103. At the time of trial initiation, the maximum feasible peramivir IM dose was 300 mg due to formulation characteristics.

Drug Administration

Subjects were confined to the study facility between Days 0-4, Days 7-11, and Days 14-18. Study drugs were administered in the morning following a 10 h fast on Days 1, 8, and 15. Peramivir was administered as an IV infusion over 15 minutes (Treatment A) or intramuscular injections in the gluteal muscle (Treatments B and C).

Investigational Product

Peramivir for IV infusion was supplied as 18 mL of 10 mg/mL (Lot CT0615) and was to be diluted in 0.9% saline to achieve a total volume of 100 mL. Peramivir for IM injection was supplied as 5 mL of 75 mg/mL in sodium citrate/citric acid buffer (Lot 06181-1) and was injected in maximum aliquots of 150 mg. Probenecid 500 mg oral tablets were supplied in a bottle of 100 tablets (b) (4) Lot 1N2568).

Key Inclusion and Exclusion Criteria

Subjects were healthy males and females between the ages of 18 and 64 years, inclusive, weighing at least 50 kg and with a BMI between 19 and 30 kg/m^2. Females of childbearing potential were surgically sterile, abstinent (from 4 weeks prior to screening through 4 weeks after last dose of study drug), on a stable regimen of hormonal contraceptives for at least 3 months), using an IUD for at least four weeks, or using barrier contraceptive with spermicide for at least four weeks. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included history of cardiovascular disease or unexplained syncope, family history of sudden death at age <55 years in a first-degree relative, or positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

The following medications and substances were disallowed while subjects were participating in the study:

- all prescription and over-the-counter medications, with the exception of acetaminophen or contraceptive medications (from within 7 days of dosing until final discharge)
- live attenuated influenza vaccine (Flumist®, from within 14 days prior to dosing until 10 days after the last dose)
- more than 10 cigarettes (or equivalent tobacco product) per day during the course of the study
- alcohol (from within 2 days prior to and during dosing)

Sample Collection

Study drug doses were administered on Days 1, 8, and 15. Blood was collected to assess peramivir concentrations in plasma predose and 0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, and 72 h postdose.

Urine was collected to assess peramivir concentrations between 0-12, 12-24, 24-36, 36-48, and 48-72 h postdose.

Nasal wash and throat gargle samples were collected to assess peramivir concentrations 2, 12, and 24 h postdose.

Analytical Plan

Pharmacokinetic data

The primary PK parameters were AUC_{inf}, AUC_{last} and C_{max}. For Treatment A (IV), an end-of-infusion concentration (i.e. C_{max}) was back-extrapolated based on peramivir concentrations in subsequent samples. Absolute bioavailability of the IM formulation was assessed by comparing Treatment B (IM) AUC_{inf} and AUC_{last} to Treatment A (IV) AUC_{inf} and AUC_{last}. Comparisons between treatment groups were evaluated by performing an analysis of variance (ANOVA), with terms for sequence, subject within sequence, period, and treatment effects on the natural log-transformed values of the primary PK parameters. Dose proportionality was assessed based on whether the 90% CI of the slope b in the model log(parameter) = a+b*log(dose) for the primary PK parameters was within the interval (0.84, 1.16).

Plasma and urine pharmacokinetic parameters were estimated by (b) (4) using a nonlinear model derived using standard noncompartmental methods (WinNonlin® v.5.2, Pharsight Corporation, Mountain View, California, USA). Predose samples that were below the limit of quantitation (BLQ) or missing samples were assigned a value of zero for AUC calculations. Visual assessment was used to identify the terminal linear phase of the concentration-time profile with a minimum of three data points; if the regression coefficient was less than 0.8, λ_z and associated parameters were considered unreliable and were not reported. The

To account for sample dilution with saline, peramivir concentrations in throat gargle and nasal wash fluids were normalized for the ratio of urea to blood urea nitrogen (BUN).

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma and urine samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Report C06-002-008). Frozen plasma samples were received between 10 and 31 Oct 2006 and stored at -80˚C. Analysis was performed between 19 Oct and 21 Dec 2006. The first day of sample collection was 3 Oct 2006, so the maximum storage sample time was 79 days, which is within the validated long-term frozen stability duration of 6 months for both plasma and urine. The LC-MS/MS methods BTM-BA 030A [plasma] and BTM-BA 033 [urine] were used. The calibration standards ranged from 1-5000 ng/mL and the quality control (QC) concentrations were 3, 250, 2000, and 4000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (plasma accuracy and precision ranges: 99.3-104% and 2-7%, respectively; urine accuracy and precision ranges: 97.0-99.5% and 4-6%, respectively).

Concentrations of peramivir in nasal wash and throat gargle samples were measured by LC-MS/MS by (b) (4) Report (b) (4) 196045). Frozen samples were received on 19 Dec 2006 and stored at -70˚C. Analysis was completed on 13 Apr 2007. The first day of sample collection was 3 Oct 2006, so the maximum storage sample time was 231 days, which is within the validated long-term frozen stability duration of 246 days for nasal wash and 301 days for throat gargle. The calibration standards ranged from 1-5000 ng/mL and the quality control (QC) concentrations were 3, 250, 2000, and 4000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (nasal wash accuracy and precision ranges: 1-3.5% and -10-7.4%, respectively; throat gargle accuracy and precision ranges: 1.4-7.7% and -14-6.0%, respectively).

Trial population

A total of 27 healthy adults between the ages of 19 and 57 were randomized in the study, evenly distributed across cohorts. All 27 subjects received study drug and were included in the pharmacokinetic and safety analysis sets. Three subjects (all males) discontinued the study prematurely: Subject 1108104 withdrew after receiving 75 mg peramivir IM due to family matters; Subject 1129207 withdrew after receiving 150 mg peramivir IV due to domestic issues; and Subject 1150309 withdrew consent after receiving 300 mg peramivir IV and IM.

Of the 27 subjects who received study drug, 85.2% of the subjects were white or Caucasian; the remainder was black or African American. More than half (63%) of the subjects were Hispanic/Latino. The majority of subjects were male (85.2%).

Plasma pharmacokinetics of a single dose of peramivir

Peramivir AUC_{last} and AUC_{inf} were comparable across peramivir treatments (IV, IM, or IM plus probenecid); as expected, peramivir C_{max} (estimated by back-extrapolation) was slightly higher following IV administration compared to IM administration (Table 1). For all three treatments, peramivir AUC_{inf} increased proportionally with increasing dose. The 90% CI for the C_{max} model slope estimates did not fall within the predefined limits

for proportionality, although slope estimates were close to 1 (0.919 and 0.912 for IV and IM administration, respectively). For all three doses (75 mg, 150 mg, and 300 mg), the mean peramivir concentration-time profiles were generally similar regardless of treatment (IV, IM, or IM plus probenecid; data not shown).

Table 1: Summary of single-dose peramivir pharmacokinetic parameters by treatment and dose group (source: Study Report Table 8)

Parameter	Dose Group	Treatment Group		
		A IV N=9	B IM N=9	C IM + Probenecid N=8
C_{max}[a] (ng/mL)	75 mg	5,740 (817)[e]	4,300 (760)	4,550 (975)
	150 mg	11,100 (2,680)	7,610 (884)[e]	7,530 (1,420)
	300 mg	20,400 (1,730)	15,200 (2,370)	15,600 (2,210)
T_{max}[b] (h)	75 mg	0.25 (0.25-0.27)[e]	0.50 (0.50-0.50)	0.50 (0.50-1.00)
	150 mg	0.25 (0.23-0.28)	0.56 (0.50-1.00)[e]	0.50 (0.50-0.50)
	300 mg	0.25 (0.23-0.28)	0.50 (0.50-0.50)	0.50 (0.50-1.00)
$AUC_{0\text{-last}}$ (ng*h/mL)	75 mg	11,000 (1,650)[e]	10,800 (1,190)	11,100 (1,350)
	150 mg	24,600 (4,000)	22,700 (3,600)[e]	21,400 (2,480)
	300 mg	47,900 (5,100)	47,200 (5,370)	50,000 (6,310)
$AUC_{0-\infty}$ (ng*h/mL)	75 mg	11,000 (1,750)[f]	10,800 (1,170)	11,000 (1,380)[f]
	150 mg	24,700 (4,010)	22,800 (3,610)[e]	21,500 (2,460)
	300 mg	48,000 (5,130)	47,300 (5,390)	50,100 (6,370)
$t_{½}$ (h)	75 mg	13.8 (2.52)[f]	25.2 (19.9)	16.5 (5.45)[f]
	150 mg	26.0 (6.33)	24.8 (3.07)[e]	25.2 (3.32)
	300 mg	21.7 (2.12)	22.8 (2.45)	21.5 (1.98)
CL[c] (mL/min)	75 mg	116 (18.1)[f]	117 (12.5)	115 (14.5)[f]
	150 mg	104 (15.6)	112 (17.2)[e]	118 (11.9)
	300 mg	105 (11.3)	107 (11.3)	101 (12.3)
V_d[d] (L)	75 mg	20.0 (2.59)[f]	265 (247)	160 (36.1)[f]
	150 mg	20.2 (3.78)	242 (53.6)[e]	257 (45.8)
	300 mg	22.4 (2.21)	211 (36.6)	187 (11.7)
CL_R (mL/min)	75 mg	105 (20.6)[g]	111 (14.1)[e]	107 (13.9)[f]
	150 mg	98.4 (29.6)[e]	101 (13.1)[e]	105 (10.4)
	300 mg	94.9 (23.5)[f]	96.5 (12.0)	93.7 (12.4)[g]
f_e (%)	75 mg	89.5 (5.7)[f]	94.9 (6.8)[e]	91.4 (6.6)
	150 mg	94.1 (18.8)[e]	90.7 (6.1)[e]	89.7 (8.0)
	300 mg	91.4 (17.3)[f]	90.4 (7.2)	94.5 (2.9)[g]

[a] Represents a back-extrapolated, rather than observed, maximum concentration for Treatment A.
[b] Presented as Median (Range)
[c] Represents CL/F for Treatment B (IM) and Treatment C (IM + Probenecid)
[d] Represents V_{ss} for Treatment A (IV) and V_z/F for Treatment B (IM) and Treatment C (IM + Probenecid).
NOTE: Vz/F overestimates the volume of distribution.
[e] N=8
[f] N=7
[g] N=6

Peramivir clearance was independent of the dose administered and correlated well with the expected average creatinine clearance in healthy individuals. Renal clearance accounted for at least 90-95% of total peramivir clearance (recovery in urine was not complete at the end of the sampling period).

The absolute bioavailability of peramivir IM ranged from 92-99% (AUC_{inf}; Table 2). Similar results were obtained for AUC_{last} (data not shown).

Table 2: Statistical assessment of peramivir IM absolute bioavailability (source: Study Report Table 12)

Parameter	Dose Group	Treatment Group[a]	N	GLS Mean[b]	Pair	Ratio[c] (%)	90% CI[d] (%)
$AUC_{0-\infty}$ (ng*h/mL)	75 mg	A	7	10,900			
		B	9	10,800	B/A	98.6	(95.6 – 101.6)
	150 mg	A	9	24,400			
		B	8	22,500	B/A	92.3	(85.1 – 100.1)
	300 mg	A	9	47,800			
		B	9	47,100	B/A	98.5	(94.9 – 102.2)

[a] Treatment A = IV infusion; Treatment B = IM injection.
[b] Geometric least squares mean.
[c] Ratio of GLS means.
[d] 90% confidence interval around the ratio of GLS means
Ln-transformed PK parameters were fitted on an ANOVA model with sequence, period, and treatment as fixed effects and subject nested within sequence as random effect.
Source: Table PKT7 of the BCX1812-111-PK Report.

Concomitant administration of oral probenecid had no statistically significant effect on peramivir exposures, with 90% CIs for AUC_{inf} and C_{max} contained between the no-effect bounds of 80-125% (Table 3).

Table 3: Statistical assessment of the effect of probenecid on peramivir pharmacokinetics (source: Study Report Table 13)

Parameter	Dose Group	Treatment Group[a]	N	GLS Mean[b]	Pair	Ratio[c] (%)	90% CI[d] (%)
C_{max} (ng/mL)	75 mg	B	9	4,230			
		C	8	4,500	C/B	106.3	(97.0 – 116.6)
	150 mg	B	8	7,550			
		C	8	7,360	C/B	97.6	(87.2 – 109.3)
	300 mg	B	9	15,000			
		C	8	15,700	C/B	104.6	(97.6 – 112.2)
$AUC_{0-\infty}$ (ng*h/mL)	75 mg	B	9	10,800			
		C	7	10,900	C/B	101.5	(98.4 – 104.6)
	150 mg	B	8	22,500			
		C	8	21,400	C/B	94.9	(87.4 – 103.0)
	300 mg	B	9	47,100			
		C	8	49,400	C/B	105.0	(101.0 – 109.2)

[a] Treatment B = IM injection; Treatment C = IM injection with co-administration of 1 g oral probenecid.
[b] Geometric least squares mean.
[c] Ratio of GLS means.
[d] 90% confidence interval around the ratio of GLS means
ln-transformed PK parameters were fitted on an ANOVA model with sequence, period, and treatment as fixed effects and subject nested within sequence as random effect.
Source: Table PKT8 of the BCX1812-111-PK Report.

Urine concentration-time data

Analysis of peramivir concentrations in urine samples supported predominantly renal excretion. Peramivir was recovered unchanged in the urine, with the majority of recovery (>85% of dose) occurring within the first 12 hours of dosing, regardless of route of administration, peramivir dose, or coadministration with probenecid (Table 4). A maximum of 95% of peramivir dose was recovered by the end of the sampling period (i.e. 72 h postdose).

Table 4: Cumulative peramivir amounts excreted in urine (source: Study Report Table 9)

Dose group	Treatment	Statistic	Cumulative Amounts (mg)				
			0-12 h	0-24 h	0-36 h	0-48 h	0-72 h
75 mg	A: IV	N Mean (SD)	8 64.18 (3.701)	7 66.39 (4.286)	7 66.69 (4.286)	7 66.96 (4.264)	7 67.11 (4.287)
	B: IM	N[a] Mean (SD)	8 66.91 (4.129)	8 70.34 (4.950)	8 70.68 (4.965)	8 70.99 (5.070)	8 71.15 (5.086)
	C: IM + probenecid	N Mean (SD)	8 62.89 (3.101)	8 67.80 (4.932)	8 68.11 (4.952)	8 68.40 (4.985)	8 68.55 (4.975)
150 mg	A: IV	N Mean (SD)	9 124.6 (14.95)	9 140.5 (26.52)	9 141.0 (26.35)	8 140.9 (28.19)	8 141.1 (28.17)
	B: IM	N Mean (SD)	8 128.8 (5.726)	8 134.9 (8.774)	8 135.3 (8.714)	8 135.8 (8.812)	8 136.0 (9.118)
	C: IM + probenecid	N Mean (SD)	8 124.9 (10.20)	8 132.9 (11.73)	8 133.5 (11.80)	8 134.1 (12.05)	8 134.5 (12.00)
300 mg	A: IV	N[a] Mean (SD)	8 246.9 (41.83)	7 270.6 (51.28)	7 272.3 (51.55)	7 273.4 (51.64)	7 274.1 (51.98)
	B: IM	N Mean (SD)	9 252.6 (20.22)	9 268.0 (21.54)	9 269.4 (21.80)	9 270.9 (21.79)	9 271.1 (21.75)
	C: IM + probenecid	N[a] Mean (SD)	7 257.4 (9.897)	7 279.3 (8.635)	7 280.6 (8.284)	6 282.5 (8.803)	6 283.3 (8.802)

[a] Outlier excluded from calculations.
Source: Table PKT2.2 from the BCX1812-111-PK Report.

Nasal wash and throat gargle concentration-time data

Peramivir concentrations were assessed in nasal wash and throat gargle samples collected 2, 12, and 24 h postdose and were normalized to urea nitrogen levels to correct for dilution of epithelial lining fluid (Figures 1 and 2, respectively). The IM and IV formulations provided comparable exposures in nasal wash as well as throat gargle samples. Peramivir concentrations in throat gargle and nasal wash samples relative to plasma increased over time, suggesting that clearance is slower from these anatomic sites than from plasma.

Figure 1: Peramivir concentrations in nasal wash samples normalized to plasma peramivir concentrations (normalized mean±SD; source: Study Report Table 10)

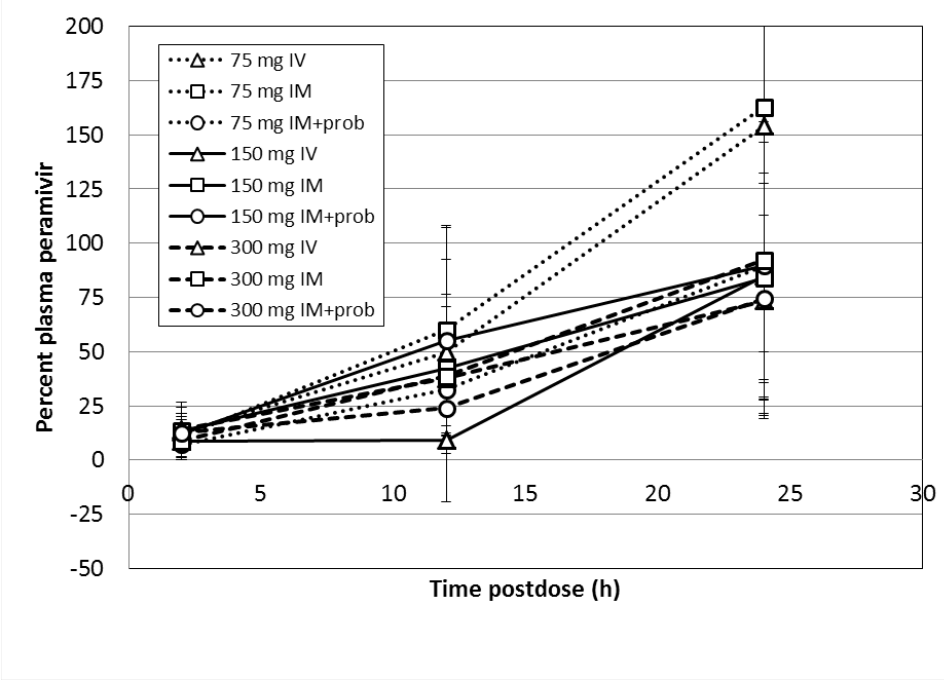
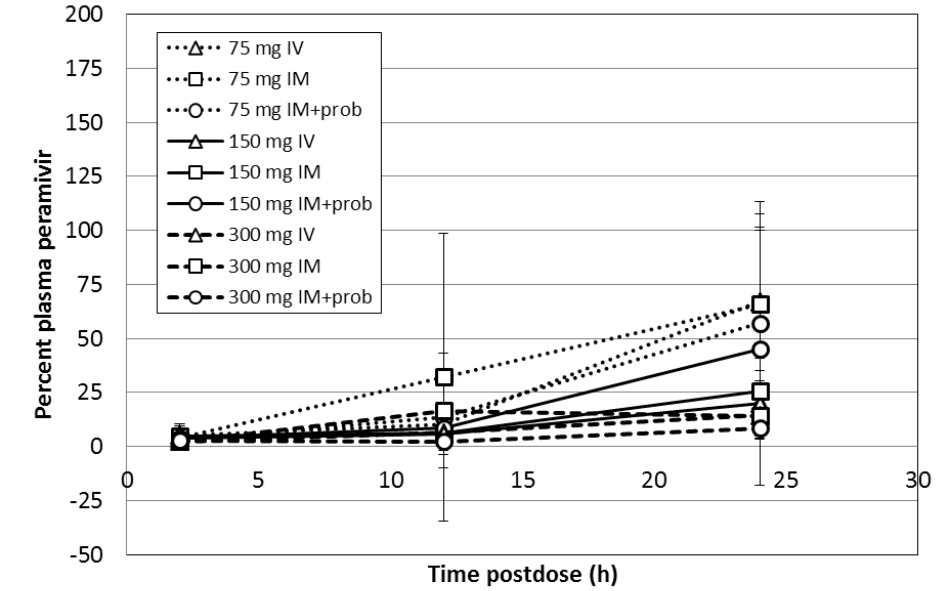


Figure 2: Peramivir concentrations in throat gargle samples normalized to plasma peramivir concentrations (normalized mean±SD; source: Study Report Table 11)



Results of safety analysis

Treatment-emergent adverse events were evenly distributed between the IV and IM administration routes and were more common in the 150 mg dose groups (24% of subject exposures were followed by a TEAE) compared to the 75 mg and 300 mg dose groups (8 and 11.5%, respectively), although numbers of subjects experiencing TEAEs were small. Headache, somnolence, and anorexia were most common, with 6.6, 3.9, and 2.6% of subject exposures followed by these TEAEs, respectively. All treatment-emergent

adverse events were Grade 1 or 2 and no subjects discontinued study drug due to adverse events. No serious adverse events or deaths occurred during the study.

Review of clinical chemistry laboratory tests revealed increases in serum creatine kinase (CK) were observed approximately 24 h following IM administration of peramivir and generally resolved within one week (similar increases have been previously observed following IM injection of drugs. The extent of the increase in serum CK was higher in the 300 mg peramivir IM dose groups (71% of subjects) compared to the 75 and 150 mg peramivir IM dose groups (0 and 6% of subjects, respectively), likely due to the number of IM injections required to administer the higher dose (two injections compared to one). No increases in serum CK were observed following peramivir IV administration.

In addition, decreases in serum uric acid were observed after administration of probenecid, consistent with its role in increasing uric acid excretion via OAT inhibition.

Trial Summary

In this study, the absolute bioavailability of peramivir IM injection was evaluated. Following IM administration, the bioavailability of peramivir was high, with the GMR for peramivir AUC_{inf} ranging from 92 to 99% with 90% confidence intervals between 80-125% for all dose groups (75, 150, and 300 mg peramivir). Increases in peramivir AUC were dose-proportional, and increases in peramivir C_{max} were approximately dose-proportional.

Peramivir was predominantly excreted unchanged in the urine. Clearance was similar to the estimated creatinine clearance in normal healthy adults and was comparable across dose levels. Coadministration of probenecid did not substantially influence peramivir pharmacokinetics, consistent with elimination via glomerular filtration without active tubular secretion.

Both the IV and IM formulations of peramivir were generally well-tolerated. IM administration of peramivir was associated with increases in serum creatine kinase in a dose-dependent manner; similar increases have been previously correlated with IM drug injections. All treatment-emergent adverse events were mild or moderate and no subjects discontinued study drug due to adverse events.

Trial BCX1812-113
An Open-Label, Randomized, Single-Center, 2-Period, Cross-Over Study to Evaluate the Relative Bioavailability and Safety of 600 mg Peramivir Administered Intramuscularly versus 600 mg Peramivir Administered Intravenously in Healthy Adult Subjects

Trial Period
6 Dec to 29 Dec 2010
Final report date: 29 Jul 2011

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. The primary goal of this study was to evaluate peramivir pharmacokinetics and bioavailability following administration of 600 mg peramivir by IV infusion or IM injection(s).

Trial Objectives
The primary objective of the trial was to:

- characterize the relative bioavaibility and pharmacokinetics of peramivir 600 mg intramuscularly (IM) versus 600 mg intravenously (IV)

The secondary objective of the trial was to:

- assess the safety and tolerability of peramivir
- determine the concentrations of peramivir present in nasal-wash and throat-gargle fluids following administration of peramivir 600 mg IM or 600 mg IV

Trial Design
This was an open-label, randomized crossover study. There were two treatments:

Treatment A peramivir 600 mg IV
Treatment B peramivir 600 mg IM

Eligible subjects were allocated to one of two treatment sequences: AB or BA. Treatments were separated by a five day washout period (at minimum). A final evaluation was performed 7 days after the second dose of study drug.

Rationale for Dose Selection
Peramivir 600 mg administered as an IV infusion was the dose evaluated in Phase 3 clinical trials. Peramivir 600 mg administered as an IM injection was previously

evaluated and bioequivalence would permit use of safety data from the IM formulation in assessment of the IV formulation.

Drug Administration

Subjects were confined to the clinic prior to study drug dosing until 24 h post-dose for both treatment periods. Study drugs were administered in the morning following a 10 h fast on Days 1, 8, and 15. Peramivir was administered as an IV infusion over 30 minutes (Treatment A) or bilateral intramuscular injections of 300 mg into the gluteal muscle (Treatments B).

Investigational Product

Peramivir for IV infusion was supplied as 20 mL of 10 mg/mL (Lot C0268) and was to be diluted in 0.9% saline to achieve a final concentration of 6 mg/mL in a total volume of 100 mL and infused within 24 h of preparation. Peramivir for IM injection was supplied as a 150 mg/mL solution in sodium citrate/citric acid buffer (Lot 7430) and was injected in maximum aliquots of 300 mg.

Key Inclusion and Exclusion Criteria

Subjects were healthy males and females between the ages of 18 and 64 years, inclusive, weighing at least 50 kg and with a BMI between 19 and 30 kg/m^2. Females of childbearing potential were surgically sterile, abstinent (from 4 weeks prior to screening through 4 weeks after last dose of study drug), on a stable regimen of hormonal contraceptives for at least 3 months), or using an IUD for at least four weeks. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included history of cardiovascular disease or unexplained syncope, positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

The following medications and substances were disallowed while subjects were participating in the study:

- all prescription and over-the-counter medications not approved by the principal investigator (prior to admission to the CRU)
- alcohol (from within 2 days prior to and during dosing)

Sample Collection

Blood was collected to assess peramivir concentrations in plasma predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 h postdose (after the injection or start of infusion).

Nasal wash and throat gargle samples were collected to assess peramivir concentrations 2, 12, and 24 h postdose.

Analytical Plan

Pharmacokinetic data

The primary PK parameter was AUC_{inf} (calculated using data up to 24 h postdose, with extrapolation of the $AUC_{24\text{-}inf}$ by C_{24}/λ); secondary parameters included $AUC_{24,}$ C_{max}, and C_{24}. Bioequivalence of AUC_{inf} was assessed using a mixed effects repeated measures analysis of variance (ANOVA), with terms for sequence, subject within sequence, period, and treatment effects on the natural log-transformed value, and was concluded if the upper and lower bounds of the 90% confidence intervals (CIs) for the geometric means of AUC_{inf} for IM and IV peramivir fell between 80 and 125%.

Pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods and statistical analyses were conducted using SAS v.9.1.3 or higher. Predose samples that were below the limit of quantitation (BLQ) or missing samples were assigned a value of zero for AUC calculations. Visual assessment was used to identify the terminal linear phase of the concentration-time profile with a minimum of three data points; if the regression coefficient was less than 0.8, λ_z and associated parameters were considered unreliable and were not reported.

To account for sample dilution with saline, peramivir concentrations in throat gargle and nasal wash fluids were normalized for the ratio of urea to blood urea nitrogen (BUN).

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma, nasal wash, and throat gargle samples were measured by LC-MS/MS by (b) (4) Report BCX1812-113-BA). Frozen plasma samples were received between 22 Dec 2010 and 27 Jan 2011 and stored at -80˚C. Analysis was performed between 5 Jan and 16 Feb 2011. The first day of sample collection was 6 Dec 2010, so the maximum storage sample time was 72 days, which is within the validated long-term frozen stability duration of 6 months, 4 months, and 16 weeks for plasma, nasal wash, and throat gargle, respectively.

The BioCryst methods BTM-BA 030, BACG-3764, and BACG-3765 were used to determine peramivir concentrations in plasma, nasal wash, and throat gargle, respectively. The calibration standards ranged from 2.5-5000 ng/mL (plasma) and 1-500 ng/mL (nasal wash and throat gargle) and the quality control (QC) concentrations were 7.5, 250, 2000, and 4000 ng/mL (plasma) and 2, 75, 250, and 400 ng/mL (nasal wash and throat gargle). All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 24 healthy adults between the ages of 22 and 61 were randomized in the study, evenly distributed across cohorts. All 24 subjects received study drug and were included in the pharmacokinetic and safety analysis sets. One subject withdrew consent after receiving 600 mg peramivir IV.

Of the 24 subjects who received study drug, 54% of the subjects were white or Caucasian, 25% were black or African American, 4% were native Hawaiian or other Pacific Islander, and 17% were categorized as Other. Just under half (42%) of the subjects were Hispanic/Latino. The majority of subjects were male (54%).

Assessment of bioequivalence of IM and IV peramivir

Peramivir AUC_{inf} was similar across peramivir treatments (IV or IM); the 90% CI of the GMR of IM peramivir to IV peramivir (97.7-103.5%) fell within the bounds of 80-125% to establish bioequivalence (Table 1). The absolute bioavailability of the IM formulation was 100.5%.

Table 1: Summary of peramivir AUC_{inf} by treatment group (source: Study Report Table 7)

	Peramivir 600 mg	
	IV (N =24)	**IM (N =23)**
$AUC_{0-\infty}$ (ng*hr/mL)		
N	24	23
Mean (SD)	102700 (18870)	102600 (19170)
Geometric Mean	101100	101000
Median	99470	97220
Min, Max	66530, 154100	66010, 153700
Coefficient of Variation	18.37	18.68
Least Square Means (90% CI)	101100 (94660, 107900)	101600 (95150, 108500)
Ratio of geometric means of IM Peramivir to IV Peramivir (90% CI)[a]	100.5% (97.7%, 103.5%)[a]	
F-test value for Sequence Effect (p-value)	<0.01 (0.9766)	
F-test value for Period Effect (p-value)	1.37 (0.2552)	

Note: ln-transformed PK parameters were fitted on an ANOVA model with fixed effects for sequence, period, and route and a random effect for subject nested within sequence.

[a] demonstrates that the 90% CI falls entirely within the interval (80.00%, 125.00%), indicating bioequivalence.

Data Source: Table 11.2

The 90% CI for the GMRs for AUC_{24} and C_{24} also fell within the bounds of 80-125% (Table 2). Peramivir C_{max} was approximately 28% higher after IV administration compared to IM (Table 2) as would be expected due to delayed distribution to the central compartment following IM injection.

Table 2: Summary of peramivir C_{max}, C_{24}, and AUC_{24} by treatment group (source: Study Report Table 8)

	Peramivir 600 mg	
	IV (N =24)	IM (N =23)
AUC_{0-24} (ng*hr/mL)		
Mean (SD)	102500 (18790)	102400 (19120)
Geometric Mean	100800	100700
Median	99170	96950
Min, Max	66410, 153600	65910, 153300
Coefficient of Variation	18.34	18.68
Least Square Means (90%) CI)	100800 (94430, 107700)	101400 (94900, 108200)
Ratio of geometric means of IM Peramivir to IV Peramivir (90% CI) [1]	100.5% (97.6%, 103.5%)[a]	
F-test value for Sequence Effect (p-value)	<0.01 (0.9766)	
F-test value for Period Effect (p-value)	1.36 (0.2560)	
$C_{24\,hr}$ (ng/mL)		
Mean (SD)	52.9 (21.1)	52.6 (19.6)
Geometric Mean	49.3	49.8
Median	48.4	46.1
Min, Max	23.7, 117	29.2, 116
Coefficient of Variation	39.9	37.2
Least Square Means (90%) CI)	49.3 (43.5, 56.0)	50.7 (44.7, 57.5)
Ratio of geometric means of IM Peramivir to IV Peramivir (90% CI) [a]		102.7% (99.5%, 106.1%) [a]
F-test value for Sequence Effect (p-value)	0.19 (0.6686)	
F-test value for Period Effect (p-value)	13.66 (0.0013)	
C_{max} (ng/mL)		
Mean (SD)	46800 (10100)	36500 (8420)
Geometric Mean	45700	35700
Median	46200	32900
Min, Max	28200, 68200	26100, 55100
Coefficient of Variation	21.5	23.1
Least Square Means (90%) CI)	45700 (42300, 49400)	35700 (33000, 38700)
Ratio of geometric means of IM Peramivir to IV Peramivir (90% CI) [a]		78.2% (73.3%, 83.3%)
F-test value for Sequence Effect (p-value)	0.06 (0.8104)	
F-test value for Period Effect (p-value)	0.45 (0.5106)	

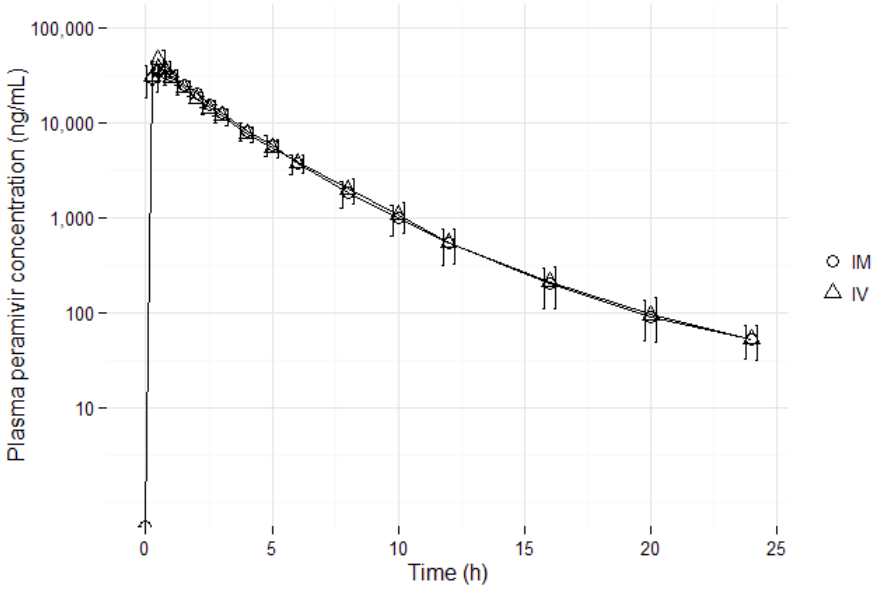
Note: ln-transformed PK parameters were fitted on an ANOVA model with fixed effects for sequence, period, and route and a random effect for subject nested within sequence.

[a] demonstrates that the 90% confidence interval falls entirely within the interval (80.00%, 125.00%), indicating equivalence.

Data Source: Table 11.2

The mean peramivir concentration-time profiles were generally similar regardless of route of administration (Figure 1). Peramivir clearance was consistent with previous estimates and correlated well with the expected average creatinine clearance in healthy individuals (data not shown).

Figure 1: Mean±SD plasma peramivir concentration-time curve



Nasal wash and throat gargle concentration-time data

Peramivir concentrations were assessed in nasal wash and throat gargle samples collected 2, 12, and 24 h postdose and were normalized to urea nitrogen levels to correct for dilution of epithelial lining fluid. Peramivir concentrations in nasal wash and throat gargle concentrations were highly variable (approximately 70-80% CV compared to 30-40% for plasma) and were generally higher in nasal wash compared to throat gargle (Figure 2). For reference, median IC_{50} values from clinical trials BCX1812-212 and 0815T0631 and the pivotal trial 0722T0621 are displayed in Figure 2. Concentrations were comparable regardless of route of administration, although were lower in both nasal wash and throat gargle compared to plasma concentrations (Figure 3).

Figure 2: Peramivir concentrations in nasal wash and throat gargle samples

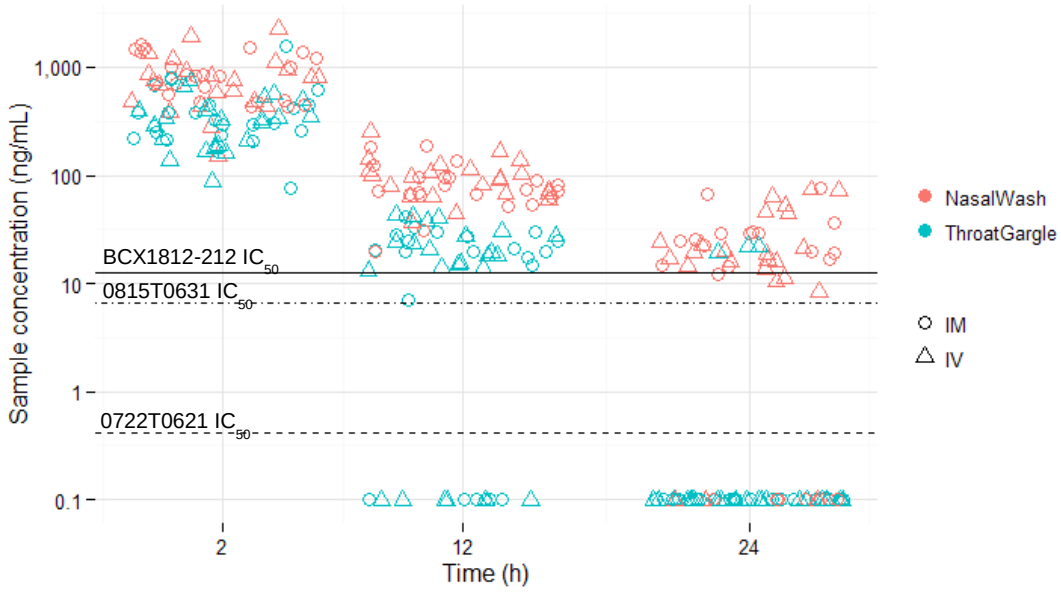
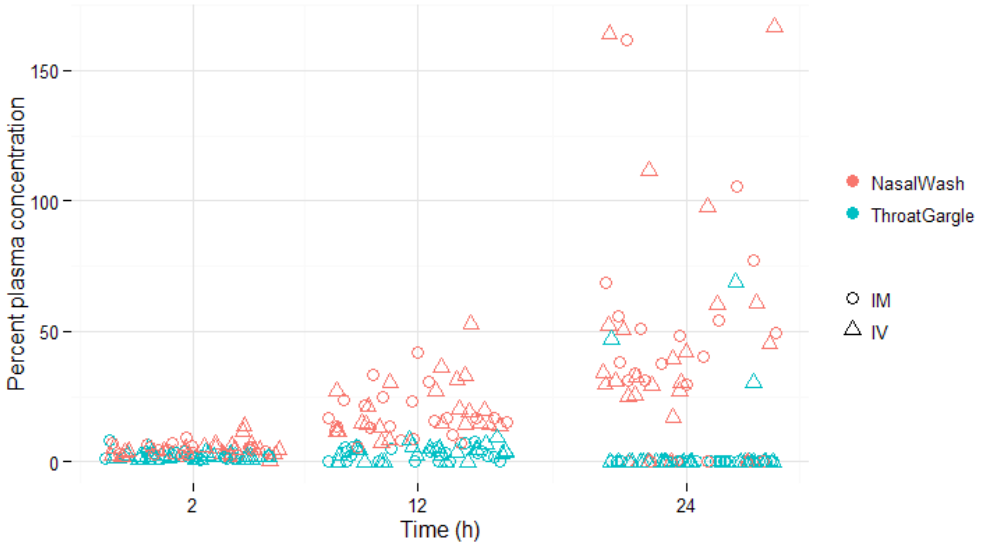


Figure 3: Peramivir concentrations in nasal wash and throat gargle samples normalized to plasma peramivir concentrations



Results of safety analysis

Treatment-emergent adverse events were more common following IM injection than IV administration (8 and 70%, respectively). The AEs reported after IV administration were moderate presyncope, mild vertigo, and mild excoriation, none of which were related to study drug administration. The AEs reported after IM injection included mild to moderate increases in blood creatine kinase (65%), mild to moderate increases in AST (39%), one moderate increase in ALT, and mild headache, all of which were categorized as related to study drug. Creatine, ALT, and AST elevations are associated with muscle injury and have been reported after intramuscular administration of drugs including peramivir.

All treatment-emergent adverse events were Grade 1 or 2 and no subjects discontinued study drug due to adverse events. No serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the absolute bioavailability of peramivir 600 mg IM injection was evaluated. Following IM administration, the bioavailability of peramivir was 100.5% with 90% confidence intervals between 97.7 and 103.5%. IM administration of peramivir was associated with increases in serum creatine kinase, ALT, and AST; similar increases have been previously correlated with IM drug injections. IV administration of peramivir was generally well-tolerated. All treatment-emergent adverse events were mild or moderate and no subjects discontinued study drug due to adverse events.

Trial BCX1812-101 (Hi-05-101)
A Phase I Double-Blind, Placebo-Controlled, Dose-Escalating Study to Evaluate the Safety and Tolerability of Intravenous Peramivir in Healthy Subjects

Trial Period
7 Mar to 5 Jun 2006
Final report date: 2 Apr 2007

Trial Site
NIH Clinical Center Critical Care Medicine Department, Bethesda, Maryland, USA

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. The primary goal of this study was to evaluate the safety, tolerability, and pharmacokinetics of peramivir following single and multiple dose intravenous administration of escalating dose levels.

Trial Objectives
The primary objective of the trial was to:

- evaluate the safety and tolerability of peramivir in healthy adults, following single- or multiple-dose intravenous administration at escalating dose levels

The secondary objective of the trial was to:

- evaluate the pharmacokinetics of intravenously administered peramivir in healthy adults, following single- or multiple-dose intravenous administration at escalating dose levels

Trial Design
This was a double-blind, randomized, placebo-controlled, dose escalating study. There were two parts (Part I: single dose; Part II: multiple dose), with five cohorts in Part I and two cohorts in Part II. Subjects in Part I were confined to the clinic for 32 to 48 hours, during which a single dose of peramivir was administered. The dose levels in Part II were to be selected based on the maximum tolerated dose based on safety data from Study Day 7 at each dose level in Part I (MTD), with Dose B equivalent to the MTD. The study schema for Parts I and II are shown in Figures 1 and 2.

Figure 1. Study schema for Part I

Description of Planned Dose Cohorts for Part I							
Cohort	Number of Subjects on Placebo	Number of Subjects on Peramivir per Dose Level (mg/kg)					Dose Increase from Previous Cohort
		0.5	1.0	2.0	3.5	5.0	
1	2	6					—
2	2		6				100%
3	2			6			100%
4	2				6		75%
5	2					6	43%
— = Not applicable							

Figure 2. Study schema for Part II

Description of Dose Cohorts for Part II			
Cohort	Number of Subjects on Placebo	Number of Subjects on Peramivir	
		Dose A	Dose B
6	4	12	
7	4		12

Only Cohort 1 of Part I was completed (Part II was not initiated and will not be discussed further in this review) due to a reevaluation of the IV peramivir Phase 1 development strategy by the Applicant. This study was terminated early in order to focus on Study Hi-06-103.

Rationale for Dose Selection

During previous development, oral peramivir was evaluated at a dose of 800 mg QD. The bioavailability was determined to be 2.3%; therefore, the calculated parenteral equivalent of 800 mg PO is 0.26 mg/kg for a 70 kg person. The starting dose of 0.5 mg/kg is approximately twice the calculated IV dose equivalent for which safety data exists from the oral peramivir development program.

Drug Administration

Subjects were confined to the clinic at 8 pm the evening prior to study drug administration until 24 h post-dose. Study drugs were administered in the morning following an overnight fast. Peramivir was administered as an IV infusion over 15 minutes.

Investigational Product

Peramivir for IV infusion was supplied as 15 mL of 10 mg/mL (lot unspecified) and was to be diluted in 0.9% saline to achieve the appropriate dose in a total volume of 75 mL and infused within 48 h of preparation.

Key Inclusion and Exclusion Criteria

Subjects were healthy males and females between the ages of 18 and 40 years, inclusive, weighing at least 50 kg and with a BMI between 19 and 32 kg/m^2. Females of childbearing potential were surgically sterile, abstinent (from 4 weeks prior to screening through 4 weeks after last dose of study drug), on a stable regimen of hormonal contraceptives for at least 3 months), or using an IUD or a condom with spermicide for at least four weeks. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included history of cardiovascular disease or unexplained syncope, positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

The following medications and substances were disallowed while subjects were participating in the study:

- all prescription and over-the-counter medications (with the exception of acetaminophen or contraceptive medications) from 7 days prior to and during dosing
- alcohol from within 2 days prior to and during dosing
- live attenuated influenza vaccine from 7 days prior to study drug administration until 14 days post-dose

Sample Collection

Blood was collected to assess peramivir concentrations in plasma predose and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 18, 24, and 48 h postdose (after the start of infusion). Urine was collected for two subsequent 24 periods postdose.

Analytical Plan

Pharmacokinetic data

Plasma C_{max}, t_{max}, AUC_{48h}, AUC_{inf}, terminal $t_{1/2}$, V_z, and CL were estimated using standard noncompartmental methods and statistical analyses using Excel, WinNonlin 4.0, and SigmaPlot. Predose samples that were below the limit of quantitation (BLQ) or missing samples were assigned a value of zero for AUC calculations. Urine A_e was calculated using Excel.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc (Birmingham, Alabama, USA; Method BTM-BA 030, Report C06-002-005). Analysis was performed between 6 and 19 Jun 2006. The first day of sample collection was 8 Mar 2006, so the maximum storage sample time was 103 days, which is within the validated long-term frozen stability duration of 6 months for plasma. The calibration standards ranged from 1-5000 ng/mL (correlation coefficient range: 0.9998-1.0000) and the quality control (QC) concentrations were 3, 250, 2000, and 4000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Concentrations of peramivir in urine samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc (Birmingham, Alabama, USA; Method BTM-BA 033, Report C06-002-005). Analysis was performed 16-17 Oct 2006. The first day of sample collection was 8 Mar 2006, so the maximum storage sample time was 222 days, which is longer than the validated long-term frozen stability duration of 6 months for urine. The calibration standards ranged from 10-50000 ng/mL (correlation coefficient: 1.0000) and the quality control (QC) concentrations were 30, 2500, 20000, and 40000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 8 healthy adults between the ages of 22 and 40 were randomized in the study. All 8 subjects received study drug and completed the study. The majority of subjects were male (62.5%) and Caucasian (75%).

Assessment of plasma peramivir pharmacokinetics

Per the Applicant, the 0.5 h postdose samples were contaminated with study drug that remained in the IV line after the infusion; therefore, the 0.5 h timepoint was not included in the estimation of PK parameters. The mean PK parameters are listed in Table 1.

Table 1: Summary of peramivir PK parameters after administration of a single dose of peramivir IV 0.5 mg/kg (source: Study Report C06-002-005-Plasma Table 3)

	Dose (mg/kg)	R^2	t½ λz (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-48hr} (hr·ng/mL)	$AUC_{0-\infty}$ (hr·ng/mL)	Vz (mL/hr/kg)	Cl (mL/hr/kg)	Study
Mean	0.5	0.960	2.9	1.00	1925.8	4993.8	4975.2	426.6	101.7	101
SD		0.052	0.53	0.0	521.1	593.4	593.4	56.8	12.0	
CV		5%	18%	0%	27%	12%	12%	13%	12%	
n		6	6	6	6	6	6	6	6	

Assessment of urinary peramivir excretion

Concentrations of peramivir in urine were assessed in the first 24 h postdose and 24-48 h postdose (Table 2).

Table 2: Amount of peramivir in urine after administration of a single dose of peramivir IV 0.5 mg/kg (source: Study Report C06-002-005-Urine Table 3)

Subject	Time (hr)	Concentration (ng/mL)	Volume (mL)	Ae (mg)	Total Ae (mg)
1001	0-24	8515	3350	28.5	28.5
1001	24-48	0.00	1830	0.0	
1002	0-24	71.9	1700	0.1	0.1
1002	24-48	0.00	1400	0.0	
1003	0-24	4405	4250	18.7	18.8
1003	24-48	51.85	2100	0.1	
1004	0-24	675.5	2100	1.4	1.6
1004	24-48	94.55	1582	0.1	
1005	0-24	14050	1600	22.5	22.6
1005	24-48	332	400	0.1	
1006	0-24	14900	4650	69.3	69.3
1006	24-48	DNR	2360		
1007	0-24	4100	2050	8.4	8.6
1007	24-48	114.5	1500	0.2	
1008	0-24	0.00	1570	0.0	0.0
1008	24-48	0.00	1600	0.0	

File Name: 1812-CLIN-101606-PeramivirHi06101-P1-2-3-4-5-6-7-8-HU

In this Reviewer's opinion, the reported amounts of peramivir excreted in urine (range: 0-69.3 mg) are inconsistent with the doses of study medication administered to each subject (range: 26.3-44.3 mg peramivir; Study Report Appendix 16) and are greater than 200% of the administered dose for 4 of 6 subjects. The reason for this inconsistency is not addressed by the Sponsor but may be due to improper storage of urine samples leading to conjugation of drug (urine sample storage conditions discussed by the Applicant in C06-002-005-Urine). In addition to the inconsistency in the calculated A_e values, the urine samples were stored for longer than the validated storage time prior to sample analysis.

Results of safety analysis

Two subjects had adverse events that were possibly related to peramivir treatment (mild elevation in serum bilirubin; mild elevation in systolic blood pressure). No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of peramivir following administration of a single dose of peramivir IV 0.5 mg/kg were evaluated. The interpretability of the estimated pharmacokinetic parameters is limited in the absence of evaluation of other doses or dosing intervals due to early termination of the study. Urinary excretion of peramivir was not comprehensively evaluated due to apparent inconsistencies with the reported doses. IV administration of peramivir was generally well-tolerated. All treatment-emergent adverse events were mild and no subjects discontinued study drug due to adverse events.

Trial BCX1812-102 (Hi-06-102)
A Phase I Double-Blind, Placebo-Controlled, Dose-Escalating Study to Evaluate the Safety and Tolerability of Intravenous Peramivir Administered Twice Daily in Healthy Subjects

Trial Period
12 Apr to 16 May 2006
Final report date: 20 Apr 2007

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. The primary goal of this study was to evaluate the safety, tolerability, and pharmacokinetics of ascending doses of intravenous peramivir following twice-daily administration for one day or 10 days.

Trial Objectives
The primary objective of the trial was to:

- evaluate the safety and tolerability of peramivir in healthy adults following intravenous administration of twice-daily doses for 1 day or 10 days at escalating dose levels

The secondary objective of the trial was to:

- evaluate the pharmacokinetics of peramivir in healthy adults following intravenous administration of twice-daily doses for 1 day or 10 days at escalating dose levels

Trial Design
This was a double-blind, randomized, placebo-controlled, dose escalating study. There were two parts (Part I: twice-daily doses for one day; Part II: twice-daily doses for 10 days), with five cohorts in Part I and two cohorts in Part II. Subjects in Part I were confined to the clinic from the evening prior to initial study drug administration until 36 hours after the second dose of study drug (approximately 2.5 days). The dose levels in Part II were to be selected based on the maximum tolerated dose based on safety data from Study Day 4 at each dose level in Part I (MTD), with Dose B equivalent to the MTD. The study schema for Parts I and II are shown in Figures 1 and 2.

Figure 1. Study schema for Part I

Description of Planned Dose Cohorts for Part I							
Cohort	Number of Subjects on Placebo	Number of Subjects on Peramivir per Dose Level (mg/kg)					Dose Increase from Previous Cohort
		0.5 b.i.d.	1 b.i.d.	2 b.i.d.	4 b.i.d.	8 b.i.d.	
1	2	6					—
2	2		6				100%
3	2			6			100%
4	2				6		100%
5	2					6	100%

Figure 2. Study schema for Part II

Description of Dose Cohorts for Part II			
Cohort	Number of Subjects on Placebo	Number of Subjects on Peramivir	
		Dose A	Dose B
6	4	12	—
7	4	—	12

Only Cohort 1 of Part I was completed (Part II was not initiated and will not be discussed further in this review) due to a reevaluation of the IV peramivir Phase 1 development strategy by the Applicant. This study was terminated early in order to focus on Study Hi-06-103.

Rationale for Dose Selection
Protocol not provided.

Drug Administration
Subjects were confined to the clinic the evening prior to study drug administration until 36 h after the start of the first infusion. Peramivir was administered as an IV infusion over 30 minutes.

Investigational Product
Protocol not submitted to NDA.

Key Inclusion and Exclusion Criteria
Protocol not submitted to NDA.

Concomitant Medications
Protocol not submitted to NDA.

Sample Collection

Blood was collected to assess peramivir concentrations in plasma predose and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 12.5 (end of second infusion), 13, 14, 15 18, 24, 36, 48, and 72 h postdose (after the start of the first infusion). Urine was collected 0-12, 12-24, 24-36, and 36-48 h after the initial infusion.

Analytical Plan

Pharmacokinetic data

Plasma C_{max}, t_{max}, AUC_{48h}, AUC_{inf}, terminal $t_{1/2}$, V_z, and CL were estimated using standard noncompartmental methods and statistical analyses using Excel, WinNonlin 4.0, and SigmaPlot. Predose samples that were below the limit of quantitation (BLQ) or missing samples were assigned a value of zero for AUC calculations. Urine A_e was calculated using Excel.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Method BTM-BA 030, Report C06-002-003). Analysis was performed between 1 May and 13 Jun 2006. The first day of sample collection was 18 Apr, so the maximum storage sample time was 56 days, which is within the validated long-term frozen stability duration of 6 months for plasma. The calibration standards ranged from 1-5000 ng/mL and 100-50000 (correlation coefficient range: 0.9999-1.0000) and the quality control (QC) concentrations were 300, 25000, and 45000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Concentrations of peramivir in urine samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Method BTM-BA 033, Report C06-002-003). Analysis was performed on 17 Oct 2006. The first day of sample collection was 18 Apr 2006, so the maximum storage sample time was 182 days, which is within the validated long-term frozen stability duration of 6 months for urine. The calibration standards ranged from 10-50000 ng/mL (correlation coefficient: 1.0000) and the quality control (QC) concentrations were 30, 2500, 20000, and 40000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

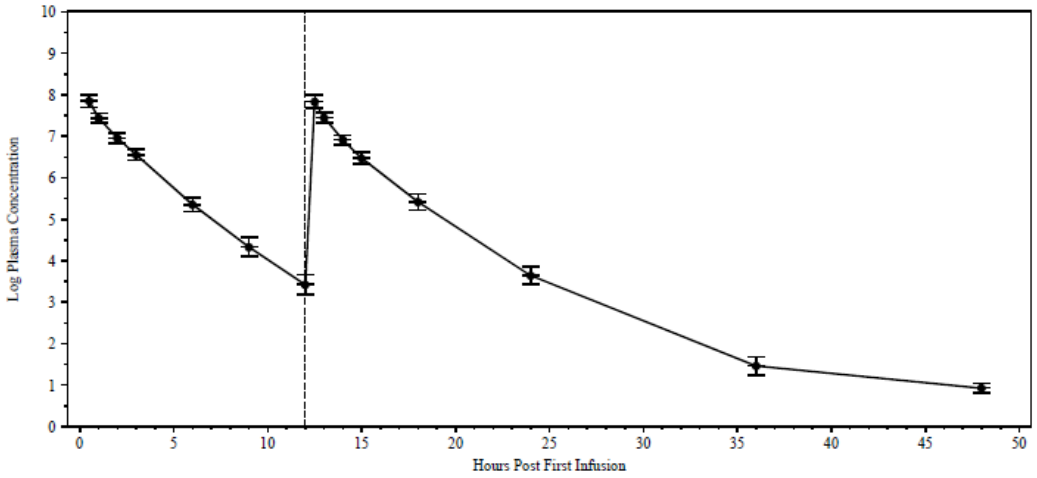
Trial population

A total of 8 healthy adults between the ages of 22 and 40 were randomized in the study. All 8 subjects received study drug and completed the study. The majority of subjects were male (75%) and Caucasian (87.5%).

Assessment of plasma peramivir pharmacokinetics

Peramivir concentration-time curves are displayed in Figure 3. Following the second dose of study drug, elimination appears to be multiphasic; therefore, the estimated terminal half-life is unlikely to be accurate as plasma samples were collected for an insufficient length of time. Peramivir PK parameters were estimated following one or two doses (spaced 12 h apart) of 0.5 mg/kg peramivir administered by IV (Table 1).

Figure 3. Mean ± SD log plasma concentration-time profiles (source: Study Report FIG_1.sas)



a: Values are summarized at their scheduled timepoints. However, only values with an actual collection time on or after the first infusion are included. Values below the detectable limit, including values of zero, were not included in the analyses.
b: Only includes subjects receiving active treatment.
NOTE: Reference line indicates the scheduled time of the second infusion.

Table 1. Summary of peramivir PK parameters after one day of twice-daily administration of peramivir IV 0.5 mg/kg (source: Study Report C06-002-003-Plasma Table 3)

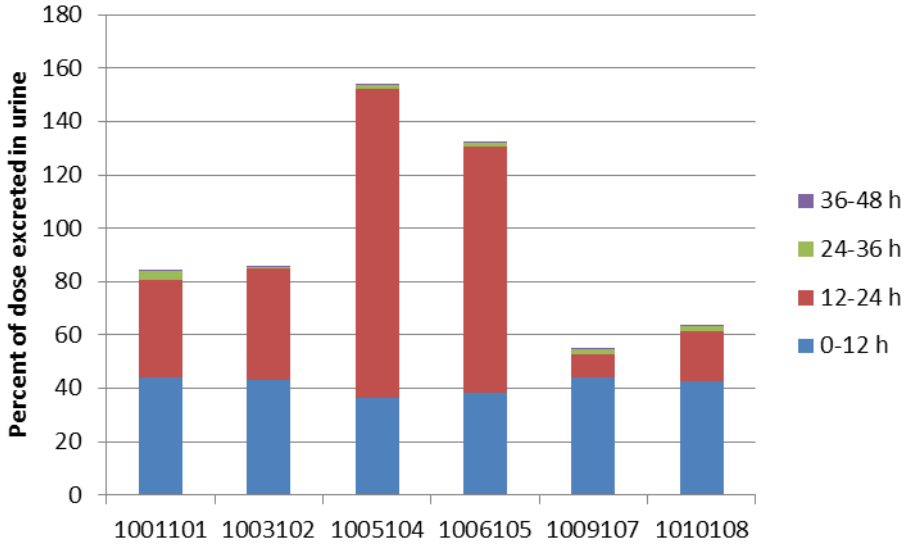
Time Period	$t_{1/2}$ λz (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}12hr}$ (hr·ng/mL)	$AUC_{0\text{-}\infty}$ (hr·ng/mL)	Volume of Distribution (ml/kg)	Clearance (mL/hr/kg)
0-12 hr	2.1±0.2	2589.2±381.5	5954.7±699.2	6046.0±704.8	251.1±38.6	83.6±8.8
CV	9.0%	14.7%	11.7%	11.7%	15.4%	10.6%
n	6	6	6	6	6	6
12-24hr	2.2±.193	2549.2±362.3	6035.9±800.8	6160.9±810.1	263.5±45.6	83.3±10.7
CV	7.8%	14.2%	13.3%	13.1%	17.3%	13.0%
n	6	6	6	6	6	6
12-72 hr	4.2±2.1	2549.2±362.3	6318.1±836.4	6256.6±837.6	335.1±79.9	81.2±11.2
CV	51.2%	14.2%	13.2%	13.4%	23.9%	13.8%
n	6	6	6	6	6	6

[a]Mean±SD

Assessment of urinary peramivir excretion

Concentrations of peramivir in urine were assessed 0-12, 12-24, 24-36, and 36-48 h after the start of the first infusion (data not shown). In two subjects, the amounts of peramivir excreted in urine (range: 27.2-125.4 mg) were higher than the dose calculated using the weight range of subjects (69.5-87.8 kg; Listing of Vital Signs, Study Report Appendix 16); of the other four subjects, two excreted approximately 80% of the total dose in 48 h and the other two excreted approximately 60% of the total dose in 48 h (Figure 4).

Figure 4. Percent of calculated peramivir dose excreted in urine after administration of two doses of peramivir IV 0.5 mg/kg 12 h apart (data source: Study Report C06-002-005-Urine Table 3)



Results of safety analysis

One subject experienced an adverse event that was possibly related to peramivir treatment (diarrhea). No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of peramivir following one day of twice-daily administration of peramivir IV 0.5 mg/kg were evaluated. The interpretability of the estimated pharmacokinetic parameters is limited in the absence of evaluation of other doses or dosing intervals due to early termination of the study. The majority of the peramivir dose had been excreted in urine 48 h after the initial dose (range: 54.8-154%). IV administration of peramivir was generally well-tolerated. All treatment-emergent adverse events were mild and no subjects discontinued study drug due to adverse events.

Trial BCX1812-103
A Phase I, Double-Blind, Placebo-Controlled, Dose-Escalating Study to Evaluate the Safety and Tolerability of Intravenous Peramivir Administered Once Daily for One Day and as Repeat Doses for Ten Days in Healthy Subjects

Trial Period
27 Apr to 30 Aug 2006
Final report date: 14 Aug 2009

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. The primary goal of this study was to evaluate the safety, tolerability, and pharmacokinetics of ascending doses of intravenous peramivir following a single dose or twice-daily administration for one and 10 days.

Trial Objectives
The primary objective of the trial was to:

- evaluate the safety and tolerability of peramivir in healthy adults following intravenous administration of a single dose for 1 day at escalating dose levels and twice-daily doses for 1 and 10 days

The secondary objective of the trial was to:

- evaluate the pharmacokinetics of peramivir in healthy adults following intravenous administration of a single dose for 1 day at escalating dose levels and twice-daily doses for 1 and 10 days

Trial Design
This was a double-blind, randomized, placebo-controlled, dose escalating study. There were two parts (Part I: single dose; Part II: twice-daily doses for 1 or 10 days), with four cohorts (evaluating ascending dose levels) in Part I and two cohorts (twice-daily administration for one or 10 days) in Part II. The dose levels in Part II were to be selected based on the maximum tolerated dose (MTD) based on safety data at Study Day 4 at each dose level in Part I. The study schema for Parts I and II are shown in Tables 1 and 2.

Table 1. Study schema for Part I

Cohort	No. of	No. of Subjects on Peramivir per Dose Level	Dose

	Subjects on Placebo	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	Increase from Previous Cohort
1	2	6				
2	2		6			100%
3	2			6		100%
4	2				6	100%

Table 2. Study schema for Part II

Cohort	No. of Subjects on Placebo	No. of Subjects on Peramivir per Dose Level		
		4 mg/kg BID (one day)	2 mg/kg BID (10 days)	4 mg/kg BID (10 days)
5	2	6		
6	9		9	9

Rationale for Dose Selection

The starting dose in Part I (1 mg/kg/day) was selected as it is less than one-tenth the human equivalent dose (14.4 mg/kg/day) of the NOAEL in non-human primates (45 mg/kg). As none of the doses evaluated in Part I met the predefined definition of MTD, the highest dose (8 mg/kg/day) was selected for the starting dose in Part II (4 mg/kg BID).

Drug Administration

In Part I, subjects were confined to the clinic the morning prior to study drug administration until 48 h after the start of the first infusion. In Part II, subjects were confined to the clinic the morning prior to study drug administration until the completion of Day 13 assessments. Peramivir was administered as an IV infusion over 15 minutes.

Investigational Product

Peramivir for IV infusion was supplied in 15 mL of a 10 mg/mL stock solution (Lots 05271-1, 06033-1, and 06047-1) and was to be diluted in 0.9% saline to achieve the appropriate dose in a total volume of 100 mL and infused within 12 h of preparation.

Key Inclusion and Exclusion Criteria

Subjects were healthy males and females between the ages of 18 and 50 years, inclusive, weighing at least 50 kg and with a BMI between 19 and 32 kg/m^2. Females of childbearing potential were surgically sterile, abstinent (from 4 weeks prior to screening through 4 weeks after last dose of study drug), on a stable regimen of hormonal contraceptives for at least 3 months), or using an IUD or a condom with spermicide for at least four weeks. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included history of cardiovascular disease or unexplained syncope,

positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

The following medications and substances were disallowed while subjects were participating in the study:

- all prescription and over-the-counter medications (with the exception of acetaminophen or contraceptive medications) from 7 days prior to and during dosing
- alcohol from within 2 days prior to and during dosing
- live attenuated influenza vaccine from 7 days prior to study drug administration until 14 days post-dose

Sample Collection

In Part I, blood was collected to assess peramivir concentrations in plasma predose; 5, 10, and 15 min postdose; and 1, 2, 3, 6, 9, 12, 18, 24, 36, 48, and 72 h postdose (after the start of the infusion). Irine was collected 0-12, 12-24, 24-36, and 36-48 h after the start of the infusion.

In Part II, Cohort 5, blood was collected to assess peramivir concentrations in plasma prior to the first dose; 5, 15, and 30 min after the first dose; 1, 2, 3, 6, 9, and 12 h after the first dose; 10, 15, and 30 min after the second dose; and 1, 2, 3, 6, 12, 24, 48, and 60 h after the second dose and 1, 2, 3, 6, 9, 12, 18, 24, 36, 48, and 72 h postdose (after the start of the infusion).

In Part II, Cohort 6, blood was collected to assess peramivir concentrations in plasma on Day 1 prior to the first dose (0800) and 0.5, 2, 6, 12, 12.5, 14, 24, 24.5, 26, and 30 h after the first dose; on Day 10 12, 24, and 48 h after the pm dose; and on Days 15 and 28 at 0800. In addition, trough samples were collected prior to the morning dose on all dosing days except for Day 10.

For both cohorts in Part II, urine was collected 0-12, 12-24, 24-36, 36-48, 48-60, and 60-72 h after the start of the first infusion.

Analytical Plan

Pharmacokinetic data

Pharmacokinetic analysis was performed by (b) (4) Plasma C_{max}, t_{max}, AUC_{12h}, AUC_{last}, AUC_{inf}, terminal $t_{1/2}$, λ_z, V_{ss}, and CL were estimated using standard noncompartmental methods with WinNonlin v.5.2 (Pharsight Corp., Mountain View, California). Attainment of steady-state was determined by comparing trough levels with an analysis of the natural log-transformed data. Dose proportionality was assessed by fitting a power model to natural log-transformed exposure parameters. Accumulation was evaluated by comparing AUC_{12h} and C_{max} on Day 1 to Day 10 and linearity was assessed by comparing AUC_{12h} on Day 10 to AUC_{inf}

on Day 1. Urine A_e, f_e, and CL_R were also estimated. Urine and predose plasma samples that were below the limit of quantitation (BLQ) were assigned a value of zero for AUC calculations.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Method BTM-BA 030, Report C06-002-003). The calibration standards ranged from 1-5000 ng/mL and 100-50000 (correlation coefficient range: 0.9999-1.0000) and the quality control (QC) concentrations were 300, 25000, and 45000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Concentrations of peramivir in urine samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Method BTM-BA 033, Report C06-002-003). The calibration standards ranged from 10-50000 ng/mL (correlation coefficient: 1.0000) and the quality control (QC) concentrations were 30, 2500, 20000, and 40000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 68 healthy adults between the ages of 18 and 47 were randomized in the study: 32 in Part I and 36 in Part II. Two subjects in Part I (one each in Cohort 1 and Cohort 4) withdrew consent during the study and one subject in Part II (Cohort 5) was discontinued due to infiltration of the study drug at the injection site; the latter subject was replaced by an additional subject. In addition, one subject in Cohort 6 (randomized to placebo) discontinued study drug due to headache and vomiting. The majority of subjects were male (69%) and Caucasian (78%).

Assessment of single-dose plasma peramivir pharmacokinetics

Mean peramivir concentration-time curves following administration of a single dose of IV peramivir are displayed in Figure 1 and PK parameters are listed in Table 3. There was a trend towards dose-proportionality for peramivir C_{max} and AUC_{12h}, AUC_{last}, and AUC_{inf} over the range evaluated, although dose-proportionality was not demonstrated statistically as the 90% CI for the slope estimates was not fully contained within 90-110%, possibly due to the small sample size. Elimination half-life increased with dose, likely because peramivir plasma concentrations were BLQ at later timepoints, resulting in an incomplete pharmacokinetic characterization of the elimination phase. Although not as pronounced as the increase in $t_{1/2}$, V_{ss} also increased with dose (range: 17.0-21.7 L).

Figure 1. Mean peramivir plasma concentration-time profiles after a single dose of IV peramivir (source: Study Report Figure 2)

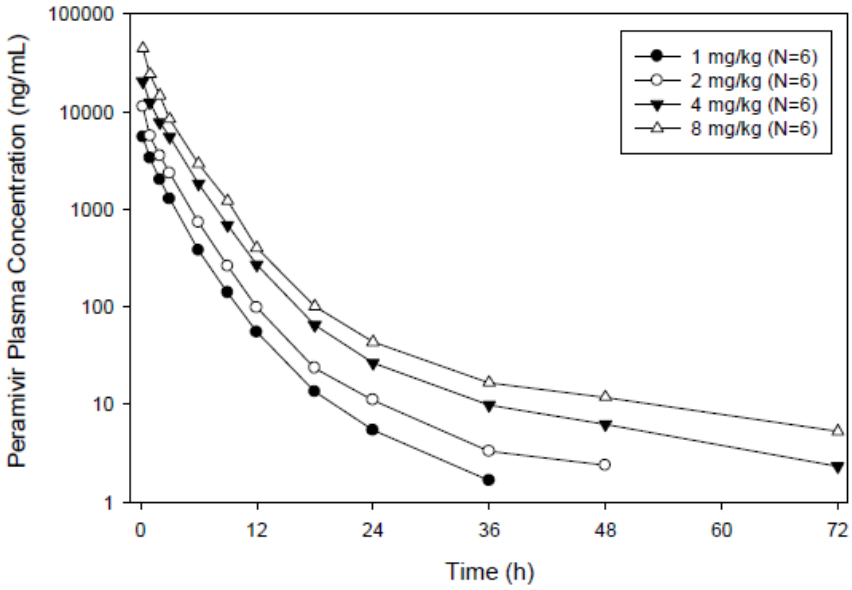


Table 3. Summary of peramivir PK parameters after a single dose of IV peramivir (source: Study Report Table 23)

Parameter	1 mg/kg (N=6)	2 mg/kg (N=6)	4 mg/kg (N=6)	8 mg/kg (N=6)
C_{max} (ng/mL)	5,552 (1,324)	11,350 (1,121)	20,490 (3,908)	44,910 (10,750)
T_{max}[1] (h)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.23-0.30)
AUC_{0-12} (ng*h/mL)	11,400 (1,660)	21,000 (2,870)	46,200 (4,460)	84,500 (21,600)
AUC_{0-last} (ng*h/mL)	11,700 (1,730)	21,600 (3,030)	47,700 (4,720)	86,900 (22,100)
$AUC_{0-\infty}$ (ng*h/mL)	11,700 (1,720)	21,600 (3,020)	47,800 (4,690)	87,000 (22,100)
$t_{½}$ (h)	7.94 (2.64)	15.5 (6.68)	19.9 (6.81)	20.7 (2.62)
CL (mL/min)	107 (24.2)	118 (9.37)	106 (6.77)	122 (18.0)
V_{ss} (L)	17.0 (3.77)	20.1 (1.29)	20.9 (2.88)	21.7 (5.62)
CL_R[1] (mL/min)	87.7 (72.5-110)	93.7 (35.3-115)	88.5 (59.5-104)	102 (36.3-122)
f_e[1] (%)	90.6 (58.5-97.0)	82.7 (30.4-86.5)	88.2 (59.1-93.3)	90.6 (24.9-94.9)

[1] Presented as Median (Range).
Source: BCX1812-103-PK

Assessment of multiple-dose plasma peramivir pharmacokinetics

Mean peramivir concentration-time curves following administration of ten days of twice-daily IV peramivir are displayed in Figure 2 and PK parameters are listed in Table 4. Accumulation with BID administration was minimal (Day 10 to Day 1 ratios for Cmax and AUC were 121.5% and 93.77%, respectively). Peramivir C_{max} and AUC_{12h} increased dose-proportionally (1.9-fold increase in both parameters with a 2-fold increase in dose).

Figure 2. Mean peramivir plasma concentration-time profiles after multiple days of peramivir IV BID (source: Study Report Figure 3)

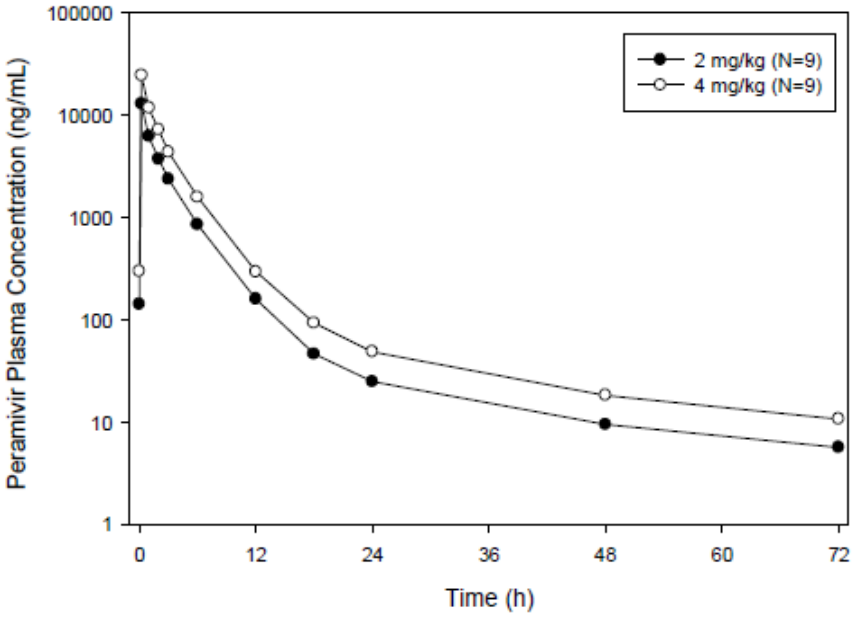


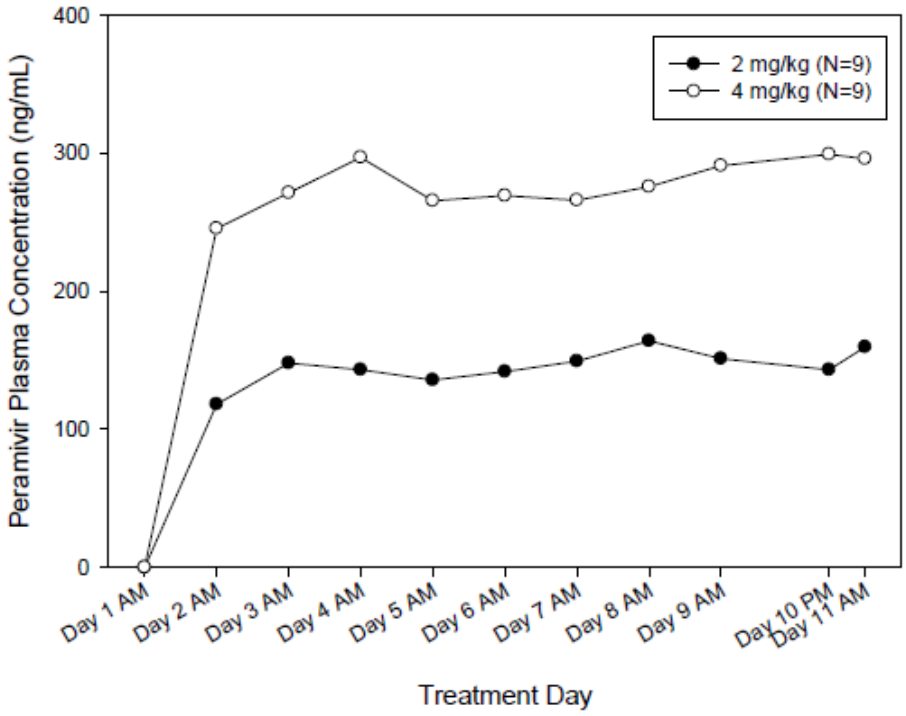
Table 3. Summary of peramivir PK parameters after multiple days of BID administration of IV peramivir in Cohort 6 (source: Study Report Table 25)

Parameter	2 mg/kg (N=9)	4 mg/kg (N=9)
C_{max} (ng/mL)	12,960 (3,121)	24,750 (3,742)
T_{max}[1] (h)	0.24 (0.22-0.25)	0.25 (0.23-0.27)
AUC_{0-12} (ng*h/mL)	23,100 (2,550)	43,600 (6,390)
$t_{½}$ (h)	22.8 (2.12)	22.6 (1.91)
CL (mL/min)	108 (4.53)	109 (12.3)
V_{ss} (L)	20.6 (2.64)	20.1 (3.08)
CL_R[1] (mL/min)	81.3 (25.8-105)	90.3 (13.2-124)
f_e[1] (%)	81.2 (22.2-98.2)	86.0 (12.8-103.3)

[1] Presented as Median (Range)
Source: BCX1812-103-PK

Time to steady-state was determined by assessing peramivir morning trough concentrations (i.e. when the trough concentration was not statistically different from the mean of the subsequent trough concentrations) and was reached by Day 3 (Figure 3). Morning and evening trough concentrations were comparable.

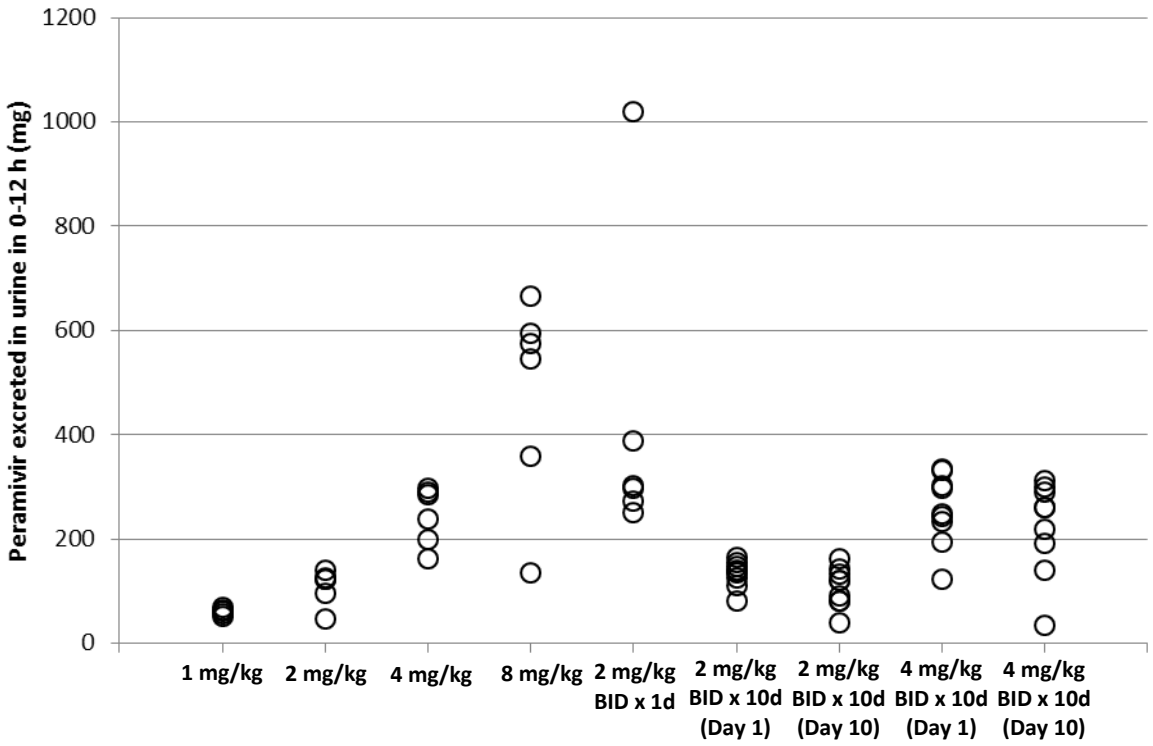
Figure 3. Mean peramivir trough concentrations after multiple days of BID administration of IV peramivir in Cohort 6 (source: Study Report Figure 4)



Assessment of urine peramivir concentrations

Concentrations of peramivir in urine were assessed over 12 hour collection periods for 48 h postdose. Urine peramivir concentrations demonstrated high interindividual variability (%CV values as high as 78.4%) and peramivir urine pharmacokinetics are therefore difficult to interpret; however, based on summary values (data not shown), the majority of peramivir was recovered unchanged in the urine in the first 12 h postdose and recovery was not yet complete 48 h postdose (although the unrecovered amount was negligible). The amount of peramivir recovered unchanged in urine increased with dose and was similar for Parts I and II (single or multiple dose administration; Figure 4).

Figure 4. Amount of peramivir excreted in urine within 12 h after administration of IV peramivir (data source: Study Report BCX1812-103-PK Tables PKT4-6)



Results of safety analysis

Four subjects (16.7%) in Part I experienced a treatment-emergent adverse event that was possibly related to peramivir treatment (two reports of headache, proteinuria, and prolonged QTC). One subject (12.5%) in Part II Cohort 5 experienced two adverse event that was possibly related to peramivir treatment (cystitis, hematuria). Eight subjects in Part II Cohort 6 experienced one adverse event that was considered probably related to peramivir treatment (drowsiness) and 11 that were considered possibly related to peramivir treatment (three reports of drowsiness, two reports of microscopic hematuria, loss of nocturnal tumescence, first degree AV block, nausea, agitation, malaise, nightmares). No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of peramivir following a single administration or one or ten days of twice-daily administration of IV peramivir were evaluated. Peramivir exposures decreased multiexponentially with a terminal elimination half-life of approximately 23 h; the volume of distribution was approximately 20-21 L. Peramivir exposures increased approximately dose-proportionally. There was little to no accumulation following multiple days of BID administration. Following single or multiple dose administration, total peramivir clearance was similar across dose levels, regardless of number of doses (range: 106-122 mL/min) and was within the range of expected creatinine clearance values in healthy subjects. Renal clearance (estimated based on urine collected within 48 h postdose) accounted for approximately 80% of total clearance. IV administration of peramivir was generally well-tolerated. All treatment-

emergent adverse events that were considered possibly or probably related to peramivir were mild or moderate and no subjects discontinued peramivir due to adverse events.

Trial BCX1812-104
A Phase I, Double-Blind, Multiple-Dose, Randomized, Placebo-Controlled, Single-Center Study to Evaluate the Safety and Pharmacokinetics of Intravenous Peramivir Administered in Elderly Subjects (≥65 Years of Age)

Trial Period
9 Aug to 15 Sept 2006
Final report date: 27 Apr 2009

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. The primary goal of this study was to evaluate the safety, tolerability, and pharmacokinetics of intravenous peramivir following multiple twice-daily administration in elderly subjects.

Trial Objectives
The primary objective of the trial was to:

- evaluate the safety and tolerability of peramivir in healthy elderly subjects following intravenous administration of multiple twice-daily doses over 1, 5, or 10 days

The secondary objective of the trial was to:

- evaluate the pharmacokinetics of peramivir in healthy elderly subjects following intravenous administration of multiple twice-daily doses over 1, 5, or 10 days

Trial Design
This was a multiple-dose, randomized, placebo-controlled, single-center study. There were two parts (Part I: twice-daily doses for a single day; Part II: twice-daily doses for 5 or 10 days), with one group (evaluating one day of dosing) in Part I and two groups (evaluating five or 10 days of dosing) in Part II. Subjects in Part I who were confirmed as eligible (based on normal urine protein measurements on Days 1 and 2) continued onto Part II (beginning on Day 3).

Part I	4 mg/kg peramivir or placebo IV over 15 min BID for 1 day
Part II, Group A	4 mg/kg peramivir or placebo IV over 15 min BID for 5 days
Part II, Group B	4 mg/kg peramivir or placebo IV over 15 min BID for 10 days

Rationale for Dose Selection

The peramivir IV dose of 4 mg/kg was previously found to be reasonably safe in Phase 1 studies. No accumulation was observed following multiple-dose administration of peramivir 4 mg/kg BID for 10 days in healthy subjects aged 18-47 years (Study Hi-06-103). The five-day duration was selected to approximate the usual duration of antiviral treatment for uncomplicated influenza and the ten-day duration was selected to evaluate the potential for extended treatment durations in certain patient subpopulations (e.g. immunocompromised patients).

Drug Administration

Peramivir was administered as an IV infusion over 15 minutes, with morning doses administered following an overnight fast.

Investigational Product

Peramivir for IV infusion was supplied in 18 mL of a 10 mg/mL stock solution (Lot CN06-066 [CT0615]) and was to be diluted in 0.9% saline to achieve the appropriate dose in a total volume of 100 mL and infused within 24 h of preparation.

Key Inclusion and Exclusion Criteria

Subjects were healthy males and females at least 65 years of age with a BMI between 19 and 32 kg/m^2 and with a Karnofsky score of at least 80. Exclusion criteria included smoking 10 or more cigarettes a day, any chronic medical problem (with the exceptions of elective surgery, outpatient surgery, osteoarthritis, controlled hypertension not requiring diuretic therapy, migraines, psoriasis with topical therapy, GERD, COPD if not receiving oral steroids, osteoporosis, stable thyroid-replacement therapy, or insomnia), history of cardiovascular disease or unexplained syncope, positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

The following medications and substances were disallowed while subjects were participating in the study:

- all prescription and over-the-counter medications (with the exception of low-dose acetaminophen, NSAIDs for arthritis, topical corticosteroids, angiotensin II receptor blocker and angiotensin I-converting enzyme inhibitors, lipid-lowering drugs, migraine treatments, topical psoriasis therapies, short-acting sedatives for insomnia, vitamins, glucosamine, chondroitin, thyroid-replacement medication if stable dose for at least 6 mos, bisphosphonates for osteoporosis, postmenopausal hormone replacement therapy) from 7 days prior to and during dosing
- alcohol from within 2 days prior to and during dosing
- live attenuated influenza vaccine from 7 days prior to study drug administration until 10 days post-dose

Sample Collection

In Part I, blood was collected to assess peramivir concentrations in plasma predose and 0.25, 1, 2, 3, 6, 9, 12, 18, 24, and 36 h postdose (after the start of the infusion). Urine was collected 0-12, 12-24, 24-36, and 36-48 h after the start of the infusion.

In Part II Group A, blood was collected to assess peramivir concentrations in plasma prior to the morning dose of study drug on Days 1-4 and prior to the last dose of study drug on Day 5 of multiple dosing. Blood samples were also collected 0.25, 1, 2, 3, 6, 12, 18, 24, and 36 h after the last dose of study drug on Day 5 of multiple dosing.

In Part II Group B, blood was collected to assess peramivir concentrations in plasma prior to the morning dose of study drug on Days 1-9 and prior to the last dose of study drug on Day 10 of multiple dosing. Blood samples were also collected 0.25, 1, 2, 3, 6, 12, 18, 24, and 36 h after the last dose of study drug on Day 10 of multiple dosing.

For both groups in Part II, urine was collected 0-12, 12-24, 24-36, 36-48, 48-60, and 60-72 h after the start of the last dose of study drug (i.e. on Day 5 for Group A and Day 10 for Group B).

Analytical Plan

Pharmacokinetic data

Plasma C_{max}, t_{max}, AUC_{12h}, AUC_{48}, AUC_{inf}, terminal $t_{1/2}$, λ_z, V_{ss}, CL, A_e, and F_e were estimated using standard noncompartmental methods with WinNonlin v.5.0.1 (Pharsight Corp., Mountain View, California) and Sigma Plot (Systat Software Inc., San Jose, California). Urine and predose plasma samples that were below the limit of quantitation (BLQ) were assigned a value of zero for all analyses.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma and urine samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Methods BTM-BA 030 [plasma] and BTM-BA 033 [urine], Report C06-002-006). Analysis was performed between 11 Sept 2006 and 15 Feb 2007. The first day of sample collection was 23 Aug 2006, so the maximum storage sample time was 176 days, which is within the validated long-term frozen stability duration of 6 months for plasma and urine. The calibration standards ranged from 1-5000 ng/mL (plasma) and 10-50000 (urine) and the quality control (QC) concentrations were 300, 25000, and 45000 ng/mL (plasma) and 30, 2500, 20000, and 40000 ng/mL (urine). All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 20 healthy adults between the ages of 65 and 79 were enrolled in and completed Part I of the study. Sixteen subjects from Part I were randomized to Group A or Group B in Part II. Of the four who were not randomized, three subjects were excluded because of a 24 h urine protein > 150 mg (collected pretreatment) and the other

subject was discontinued because only 16 subjects were required for Part II. All subjects who were enrolled in Part II completed Part II of the study. Half of the subjects in Part I and 62.5% of the subjects in Part II were male; 95% of subjects in Part I and 100% of subjects in Part II were Caucasian, with just under half of the subjects in both parts self-identifying as Hispanic/Latino.

Assessment of plasma peramivir pharmacokinetics

The pharmacokinetic parameters of peramivir following one, five, or ten days of twice-daily IV dosing of 4 mg/kg over 15 minutes are displayed in Table 1. Mean AUC_{12} and C_{max} values were comparable across dosing durations, suggesting no accumulation of peramivir following twice-daily dosing in healthy elderly subjects.

Table 1. Key peramivir pharmacokinetic parameters (source: Study Report Table 9)

Parameter	After First Dose Part I (All Subjects) n = 20	After Last Dose over 5 Consecutive Days (Part II, Group A) n = 6	After Last Dose over 10 Consecutive Days (Part II, Group B) n = 6
C_{max} (ng/mL)			
Mean	22,647.5	22,608.3	22,933.3
SD	4823.7	4910.7	2951.2
% CV	21.3%	21.7%	12.9%
Range	12,050 – 31,200	15,400 – 30,250	17,600 - 25850
$AUC_{(0\text{-}12\ hrs)}$ (ng•hr/mL)			
Mean	61,334.0	70465.4	61572.3
SD	8793.4	12,236.4	8564.4
% CV	14.3%	17.4%	13.9%
Range	44,609 – 76,978.8	57,322.6 – 82,950.0	44,754.0 – 67,885.4
$AUC_{(0\text{-}48\ hrs)}$ (ng•hr/mL)	ND[a]		
Mean		78,950.1	67,425.4
SD		15,001.3	9965.5
% CV		19.0%	14.8%
Range		63,589.4 – 96,148.2	48,007.8 – 74,760.8
CLss (mL/hr/kg)	ND[a]		
Mean		58.2	66.3
SD		10.2	11.5
CV		17.6%	17.4%
Range		48.2 – 69.8	58.9 – 89.4
CLss (mL/min)	ND[a]		
Mean		79.5	77.7
SD		13.1	15.4
CV		16.5%	19.8%
Range		56.4 – 91.6	59.5 – 98.9
Vss (mL/kg)	ND[a]		
Mean		267.7	270.2
SD		28.6	31.7
CV		10.7%	11.7%
Range		233.1 – 304.0	241.0 – 329.8

[a] These assessments were not performed.
Source: Appendix 7 of BioCryst Bioanalytical Report C06-002-006

Plasma pharmacokinetics of the peramivir IV dose of 4 mg/kg BID for a single or multiple days was evaluated in healthy non-elderly subjects between the ages of 18 and 47 years in study BCX1812-103 (Peramivir Hi-06-103). Key PK parameters from both elderly (current study) and non-elderly (BCX1812-103) are listed in Table 2. While mean C_{max} values were similar between the two populations, mean AUC values were about 30% higher in elderly subjects after one and 10 days of twice-daily dosing likely because of slower peramivir clearance due to natural decreases in renal function with age.

Table 2. Mean±SD key peramivir pharmacokinetic parameters from elderly and non-elderly subjects (source: Study Report 2 Table 1 and BCX1812-103 study report)

Days of dosing (4 mg/kg BID)	C_{max} (ng/mL)	AUC_{12h} (ng.h/mL)	CL (mL/min)
Non-elderly (BCX1812-103)			
1	20490 (3908)	47800 (4690)	106 (6.77)
10	24750 (3742)	43600 (6390)	109 (12.3)
Elderly (BCX1812-104)			
1	22647.5 (4823)	61334.0 (8793)	-
5	22608.3 (4910)	70465.4 (12236)	79.5 (13.1)
10	22933.3 (2951)	61572.3 (8564)	77.7 (15.4)

Assessment of urine peramivir pharmacokinetics

Most of the peramivir dose (mean 81.2%, SD 11.0%) was recovered in the urine over the initial 48 h period following the first dose.

Results of safety analysis

One subject in Part I experienced a treatment-emergent adverse event (drowsiness) that was identified by the investigator as probably related to peramivir treatment. One subject in Part II experienced an adverse event (somnolence) that was deemed probably related to peramivir treatment. No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of peramivir following a single day or five or ten days of twice-daily administration of 4 mg/kg IV peramivir were evaluated in healthy elderly subjects. Mean peramivir AUC_{12} values were approximately 30% higher compared to historical data in healthy non-elderly subjects; there was a corresponding decrease in clearance (approximately 25% lower in elderly subjects compared to non-elderly). IV administration of peramivir was generally well-tolerated. All treatment-emergent adverse events that were considered possibly or probably related to peramivir were mild and no subjects discontinued peramivir due to adverse events.

Trial BCX1812-105
A Phase I, Open-Label, Multi-Center Study to Evaluate the Safety and Pharmacokinetics of Intravenous Peramivir (2 mg/kg) Administered in Subjects with Impaired Renal Function

Trial Period
11 Oct 2006 to 26 Mar 2007
Final report date: 23 June 2009

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. Peramivir is predominantly excreted renally. The primary goal of this study was to evaluate the effect of renal impairment (RI) on the pharmacokinetics of peramivir following intravenous administration and to assess the effect of hemodialysis on the pharmacokinetics of peramivir in patients with end-stage renal disease (ESRD).

Trial Objectives
The primary objective of the trial was to:

- evaluate the safety of intravenously administered peramivir in subjects with renal impairment

The secondary objectives of the trial were to:

- evaluate the effect of varying degrees of renal impairment on the pharmacokinetics of intravenously administered peramivir
- evaluate the effect of hemodialysis on the pharmacokinetics of intravenously administered peramivir in patients with end-stage renal disease

Trial Design
This was an open-label study with five cohorts defined by renal function.

Cohort 1	Normal renal function (CL_{CR} >80 mL/min)
Cohort 2	Mild renal impairment (CL_{CR} 50-80 mL/min)
Cohort 3	Moderate renal impairment (CL_{CR} 30-49 mL/min)
Cohort 4	Severe renal impairment (CL_{CR} <30 mL/min)
Cohort 5	End-stage renal disease requiring chronic hemodialysis

Subjects in Cohorts 1-4 received a single dose of intravenous peramivir 2 mg/kg, while subjects in Cohort 5 received single doses of intravenous peramivir 2 mg/kg on two separate occasions: once 2 h before hemodialysis and once at the end of a subsequent hemodialysis. Subjects were confined to the clinic on Day 0 until completion of PK and safety assessments on Day 4 (72 h postdose). Subjects in Cohort 5 were also confined to the clinic from the morning of Day 11 until the morning of Day 15.

Rationale for Dose Selection

The peramivir IV dose of 4 mg/kg was previously found to be reasonably safe in Phase 1 studies; a reduced dose of 2 mg/kg was selected for this renal impairment study based on characterization of peramivir clearance as predominantly renal.

Drug Administration

Peramivir was administered as an IV infusion over 15 minutes, with doses administered in the morning. Subjects were asked to fast (if possible) from 10 h prior to study drug administration until 2 h after study drug administration.

Investigational Product

Peramivir for IV infusion was supplied in 18 mL of a 10 mg/mL stock solution (Lot CT0615) and was to be diluted in 0.9% saline to achieve the appropriate dose in a total volume of 100 mL and infused within 24 h of preparation.

Key Inclusion and Exclusion Criteria

Subjects were healthy males and females at least 18 years of age with a BMI between 19 and 38 kg/m^2 and with normal renal function or a history of stable renal impairment. Females of childbearing potential were surgically sterile, abstinent (from 4 weeks prior to screening through 4 weeks after last dose of study drug), on a stable regimen of hormonal contraceptives for at least 3 months), or using an IUD or a condom with spermicide for at least four weeks. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included renal carcinoma or transplantation within one year prior to Screening, positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

Concomitant medications to treat underlying disease states or medical conditions related to renal insufficiency were permitted.

The following medications and substances were disallowed while subjects were participating in the study:

- live attenuated influenza vaccine (FluMist) from 14 days prior to study drug administration until 10 days post-dose
- live attenuated influenza vaccine (FluMist) at any time during the current influenza season (for subjects 65 years and older)

Sample Collection

For subjects in Cohorts 1-4, blood was collected to assess peramivir concentrations in plasma predose and 0.25 (end of infusion), 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120, 144 and 168 h postdose (after the start of the infusion) on Day 1. Urine was collected predose (-24 to 0 h) and at 0-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h postdose.

For subjects in Cohort 5, blood was collected predose and 0.25 (end of infusion), 1, 2, 3, 6, 9, 12, 24, 36, 48, and 72 h from the same arm to which the infusion was administered on Days 1 and Day 12. Arterial (pre-dialysis) and venous (post-dialysis) samples were also collected 3, 4, 5, and 6 h post-infusion. (Dialysis occurred approximately 2 h post-infusion and lasted for approximately 4 h and Days 1 and 3 [between 48 and 72 h sample collection].) Urine was not collected in Cohort 5.

Analytical Plan

Pharmacokinetic data

Plasma C_{max}, t_{max}, AUC_{last}, AUC_{inf}, terminal $t_{1/2}$, λ_z, V_{ss}, CL, A_e, and extraction ratio (Cohort 5 Dose 1 only) were estimated using standard noncompartmental methods with WinNonlin v.5.0.1 (Pharsight Corp., Mountain View, California) and Sigma Plot (Systat Software Inc., San Jose, California). Urine A_e, f_e, and CL_R were derived from the urine concentrations. Urine and predose plasma samples that were below the limit of quantitation (BLQ) were assigned a value of zero for all analyses.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma and urine samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Methods BTM-BA 030A [plasma] and BTM-BA 033 [urine], Report C06-002-009). Analysis was performed between 27 Nov 2006 and 19 Apr 2007. The first day of sample collection was 23 Oct 2006, so the maximum storage sample time was 178 days, which is within the validated long-term frozen stability duration of 6 months for plasma and urine. The calibration standards ranged from 1-5000 ng/mL (plasma) and 10-50000 (urine) and the quality control (QC) concentrations were 300, 25000, and 45000 ng/mL (plasma) and 30, 2500, 20000, and 40000 ng/mL (urine). All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 30 subjects (six in each cohort) were enrolled in and completed the study. The demographics for each cohort are listed in Table 1.

Table 1. Demographic summary (source: Study Report Table 6)

		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
CL_{CR} (mL/min)	Range	80.7-150.9	56.5-85.9	32.3-43.5	12.7-26.8	requiring dialysis
Age (y)	Mean	52	56.3	56.8	64.0	51.5

	(range)	(41-64)	(44-70)	(28-76)	(54-75)	(37-60)
Male sex	N (%)	4 (66.7)	2 (33.3)	2 (33.3)	3 (50.0)	4 (66.7)
Caucasian	N (%)	4 (66.7)	4 (66.7)	4 (66.7)	2 (33.3)	1 (16.7)
Black/Afr Am	N (%)	1 (16.7)	2 (33.3)	1 (16.7)	4 (66.7)	5 (83.3)
Hispanic	N (%)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Am	N (%)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)

Two subjects (1001 [Cohort 2] and 1002 [Cohort 4]) were excluded from the PK analysis because the infusion durations (55 and 39 minutes, respectively) were longer than the protocol-specified duration of 15 min.

Assessment of plasma peramivir pharmacokinetics

The peramivir concentration-time profiles following a single IV administration of peramivir 2 mg/kg over 15 minutes in subjects with normal renal function; mild, moderate, or severe renal impairment; or end-stage renal disease 2 h before or immediately after hemodialysis are displayed in Figure 1 and pharmacokinetic parameters are listed in Table 2. Note that due to the duration of PK sampling in the ESRD groups, estimation of half-life and dependent parameters (e.g. AUC) may not be reliable.

Figure 1. Mean peramivir plasma concentration-time profiles by renal function group (semilog scale; source: Study Report Figure 1)

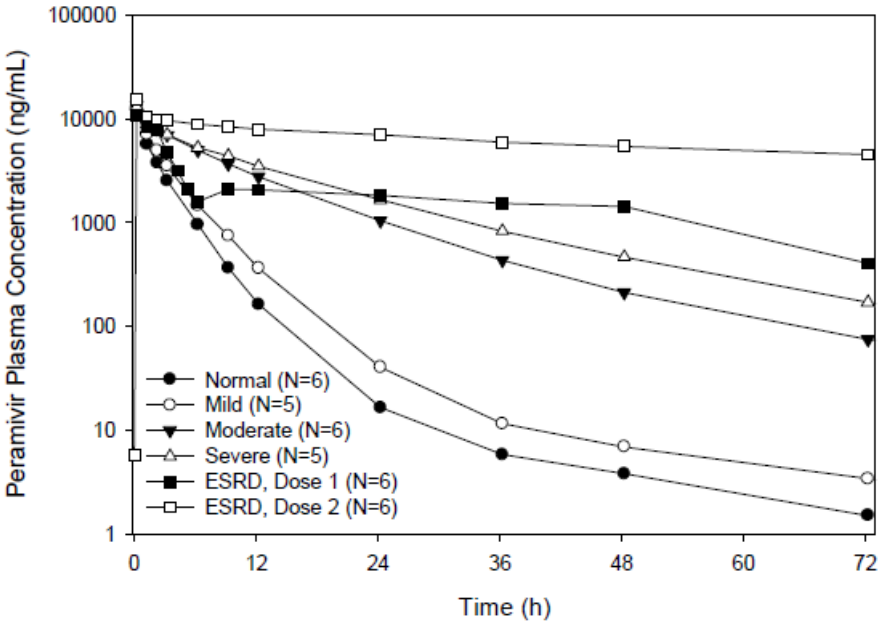


Table 2. Key peramivir pharmacokinetic parameters (source: Study Report Table 9)

Parameter	Renal Function Group					
	Normal (N=6)	Mild (N=5)[4]	Moderate (N=6)	Severe (N=5)[4]	ESRD	
					Dose 1 (N=6)	Dose 2 (N=6)
C_{max} (ng/mL)	12,800 (2,860)	12,500 (3,590)	13,700 (3,780)	13,200 (2,910)	11,000 (3,000)	15,500 (3,610)
T_{max}[1] (h)	0.25 (0.25-0.30)	0.25 (0.23-1.00)	0.25 (0.23-0.32)	0.25 (0.25-0.28)	0.25 (0.25-2.25)	0.25 (0.25-1.25)
$AUC_{0\text{-last}}$ (ng*h/mL)	26,000 (3,200)	33,900 (7,870)	108,000 (31,200)	136,000 (40,600)	107,000[2] (20,300)	470,000[3] (81,200)
$AUC_{0-\infty}$ (ng*h/mL)	26,000 (3,180)	33,900 (7,880)	108,000 (31,200)	137,000 (41,100)	ND	ND
$t_{½}$ (h)	20.7 (4.78)	23.7 (2.84)	28.7 (3.21)	30.7 (2.75)	70.6[2] (33.9)	93.1[3] (53.3)
CL (mL/min)	108 (9.90)	77.9 (21.4)	26.8 (5.35)	21.1 (4.68)	ND	ND
V_{ss} (L)	22.0 (4.35)	20.6 (6.07)	21.9 (3.40)	23.5 (2.80)	ND	ND
CL_{CR} (mL/min)	97.1 (9.23)	66.3 (15.8)	23.2 (5.59)	14.7 (3.27)	ND	ND
f_e (%)	90.4 (7.5)	86.0 (8.5)	85.9 (5.5)	71.6 (16.4)	ND	ND

[1] Presented as Median (Range)
[2] Parameter is truncated to 48 hours post-infusion.
[3] Parameter is truncated to 72 hours post-infusion.
[4] Subjects 1001 (mild renal impairment) and 1002 (severe renal impairment) are excluded as the actual duration of infusion was longer than 15 minutes due to pump malfunction.
ND = not done.
Source: BCX1812-105-PK Report.

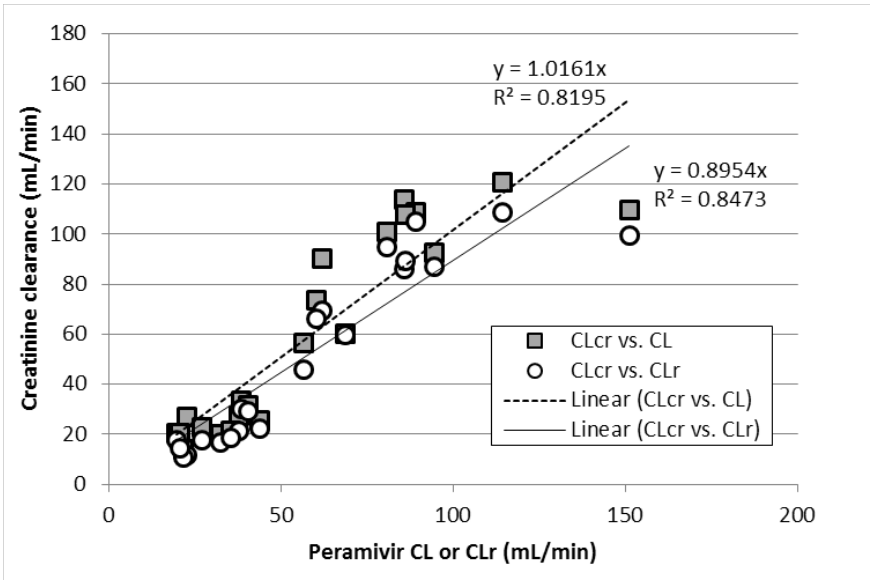
Maximum peramivir concentrations in plasma were reached directly after the infusion in most patients, with comparable mean C_{max} values across renal function groups. Mean AUC values increased with decreasing renal function due to impaired clearance (evident in increasing half-life); this observation was expected based on the characterization of renal clearance as the primary route of elimination in this and other studies (e.g. renal clearance accounted for approximately 90% of total clearance in subjects with normal renal function in this study).

Reviewer's comment: Hemodialysis significantly reduced systemic peramivir exposure in subjects with ESRD by approximately 77%. Please refer to the QBR for further discussion about peramivir dosing in ESRD patients undergoing hemodialysis.

The correlation between creatinine clearance and peramivir total and renal clearance is shown in Figure 2. Both clearance and renal clearance correlated well with creatinine

clearance. The similarity of the two relationships underscores the primacy of renal clearance in peramivir elimination. The slope of the linear relationship between renal clearance and creatinine clearance was 0.9, suggesting that peramivir is primarily eliminated via glomerular filtration (i.e. active tubular secretion and/or reabsorption do not appear to substantially contribute to peramivir elimination).

Figure 2. Correlation between creatinine clearance and peramivir renal or total clearance (source: Study Report Tables PKT3 and PKT4)



A statistical comparison of peramivir pharmacokinetic parameters is shown in Table 3. After a single dose of IV peramivir, C_{max} was not substantially impacted by renal impairment, but systemic peramivir exposures (AUC) increased with the degree of renal dysfunction (4- and 5-fold increases in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function).

Table 3. Statistical comparison of peramivir plasma pharmacokinetics between renal function groups (source: Study Report Table 5)

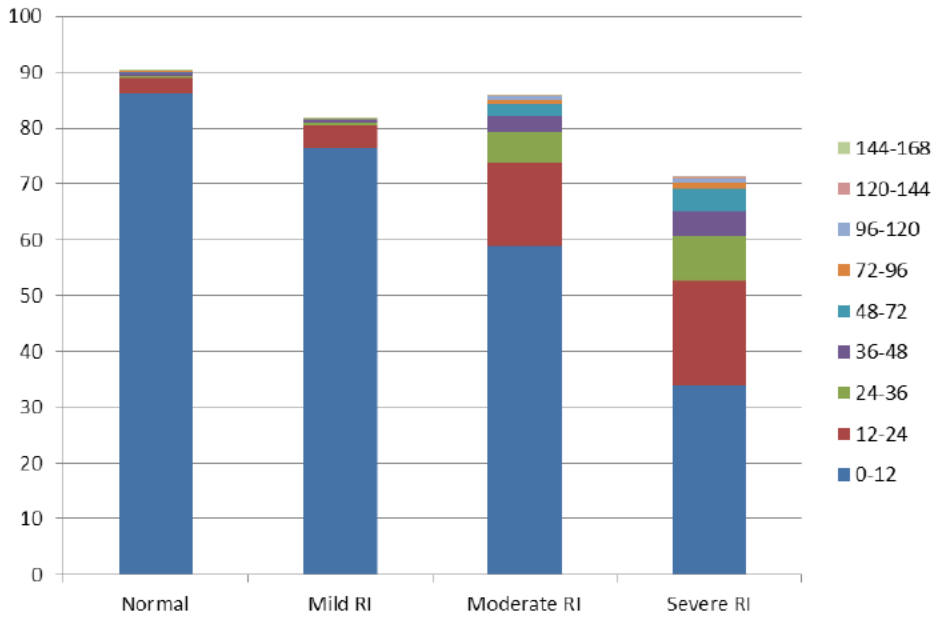
Parameter	Renal Group	N	GLS Mean[1]	Pair	Ratio[2] (%)	90% CI[3] (%)
C_{max} (ng/mL)	Normal	6	12,500			
	Mild	5	12,000	Mild/Normal	96.0	(73.3 – 125.9)
	Moderate	6	13,200	Moderate/Normal	105.6	(81.6 – 136.6)
	Severe	5	12,900	Severe/Normal	103.3	(78.8 – 135.4)
	ESRD, Dose 1	6	10,700	ESRD, Dose1/Normal	85.6	(66.1 – 110.7)
	ESRD, Dose 2	6	15,100	ESRD, Dose2/Normal	120.4	(93.0 – 155.9)
$AUC_{0\text{-last}}$ (ng*h/mL)	Normal	6	25,800			
	Mild	5	33,100	Mild/Normal	128.1	(98.7 – 166.3)
	Moderate	6	104,000	Moderate/Normal	401.6	(313.2 – 514.8)
	Severe	5	131,000	Severe/Normal	508.4	(391.7 – 659.8)
$AUC_{0-\infty}$ (ng*h/mL)	Normal	6	25,900			
	Mild	5	33,100	Mild/Normal	128.0	(98.6 – 166.2)
	Moderate	6	104,000	Moderate/Normal	401.8	(313.3 – 515.2)
	Severe	5	132,000	Severe/Normal	511.7	(394.2 – 664.2)

[1] Geometric least squares mean.
[2] Ratio of GLS means.
[3] 90% confidence interval around the ratio of GLS means
Log transformed PK parameters were fitted on an ANOVA model with cohort as fixed effect.
Subjects 1001 (mild renal impairment) and 1002 (severe renal impairment) are excluded as the actual duration of infusion was longer than 15 minutes due to pump malfunction.
Source: Table PKT5.

Assessment of urine peramivir concentrations

Urinary peramivir was not assessed in patients with ESRD undergoing hemodialysis as it was anticipated that urinary excretion would be minor in these subjects. Analysis of the mean percent of the peramivir dose excreted in urine over time showed that while the majority of the peramivir dose (at least 70%) was excreted over 168 h even in subjects with severe renal impairment, renal clearance was slower in subjects with a greater degree of renal dysfunction (Figure 3).

Figure 3. Mean peramivir f_e (as a percent) by urine collection interval (h postdose) (source: Study Report BCX1812-105-PK Listing PKL3)



Simulation of multiple-dose administration

The Sponsor performed simulations of once- or twice-daily administration of peramivir (dose adjusted for renal function) to patients with renal impairment using a three-compartment model fitted to PK profiles from subjects with normal renal function or mild, moderate, or severe renal impairment in the current study.

Peramivir 600 mg QD for five days was used as the reference treatment in healthy subjects. No dose adjustment was proposed for subjects with mild renal impairment (CL_{CR} ≥50 mL/min) as the observed increase in peramivir AUC (28%) was not considered clinically relevant. Dose reductions (one-fourth to one-sixth) were proposed to account for the 4- and 5-fold increases in peramivir AUC in subjects with moderate and severe renal impairment, respectively. Target exposures included a steady-state C_{max} not greater than that observed in subjects with normal renal function, a steady-state AUC_{24} of 100,000 ng.h/mL, and a steady-state C_{trough} of at least 80 ng/mL to ensure sufficient antiviral activity. The proposed reduced doses (b) (4) for patients with moderate and severe renal impairment, respectively) and predicted exposures are listed in Table 4. (b) (4)

Table 4. Predicted steady-state peramivir exposures at proposed doses for multiple dose administration in patients with renal impairment (source: BCX1812-105 PK Study Report Table 7)

Renal Function Group	Proposed Regimen (b) (4)	C_{min} (ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
Normal (CL_{CR} > 80 mL/min)		69.6 392	41,400 21,000	82,800 82,800
Mild (CL_{CR} = 50–80 mL/min)		152 732	41,200 21,200	97,800 97,800
Moderate (CL_{CR} = 30–49 mL/min)		979 1,810	12,500 7,560	80,900 80,800
Severe (CL_{CR} = 10-29 mL/min)		1,340 2,090	9,110 5,960	78,200 78,100
ESRD (Hemodialysis or CL_{CR} < 10 mL/min)		NA[2]	NA[2]	NA[2]

[1] When administered on a dialysis day, peramivir should be administered after hemodialysis.
[2] Exposure parameters are not available because a PK model was not developed in this subject population.
Source: Sections 12.2.2.1 and 12.2.2.2.

Reviewer's comment: At the time of completion of the current study, (b) (4) *The dose proposed in the current NDA submission under review is a single administration of peramivir 600 mg. Please refer to the QBR and the Pharmacometrics Review for a discussion about peramivir dose reduction in patients with creatinine clearance below 50 mL/min.*

Assessment of peramivir protein binding

The extent of plasma protein binding was evaluated in plasma samples collected predose, to which peramivir was added to final concentrations of 4.5, 45, and 4500 ng/mL (for reference, the mean C_{max} in subjects with normal renal function was 12,800 ng/mL). Peramivir plasma protein binding was low in all renal function groups (range: 0-4.9%) and independent of peramivir concentration and renal function.

Results of safety analysis

There were seven treatment-emergent adverse events reported during the study that were categorized as possibly (diarrhea, nasopharyngitis, gout, pain in extremity, headache) or probably (facial neuralgia, somnolence) related to study treatment; all were mild or moderate in severity. There was no relationship between degree of renal impairment and incidence of TEAE. No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of peramivir following a single intravenous administration of 2 mg/kg IV peramivir were evaluated in subjects with normal renal function; mild, moderate, or severe renal impairment; or ESRD before or after dialysis. While C_{max} was not substantially affect by renal dysfunction, the mean peramivir AUC_{inf} values were approximately 1.3-, 4.0, and 5.1-fold higher compared to subjects with

normal renal function; with increasing renal dysfunction there was a corresponding decrease in clearance. Because of the increases in systemic peramivir exposures and the likelihood of accumulation after multiple dosing in patients with moderate or severe renal impairment, (b) (4) Because simulated exposures following a single 600 mg dose are higher than what has been previously evaluated, the Clinical Pharmacology Review Team recommends a dose reduction in patients with creatinine clearance below 50 mL/min (please refer to the QBR and the Pharmacometrics Review for further discussion). Due to logistical constraints on PK sampling times in subjects undergoing hemodialysis, accurate systemic exposures (AUC) could not be estimated; however, available data indicate that hemodialysis removes peramivir from systemic circulation, so peramivir should be administered post-hemodialysis in subjects with ESRD. IV administration of peramivir was generally well-tolerated. All treatment-emergent adverse events that were considered possibly or probably related to peramivir were mild or moderate in severity and no subjects discontinued peramivir due to adverse events.

Trial BCX1812-105
A Phase I, Open-Label, Multi-Center Study to Evaluate the Safety and Pharmacokinetics of Intravenous Peramivir (2 mg/kg) Administered in Subjects with Impaired Renal Function

Trial Period
11 Oct 2006 to 26 Mar 2007
Final report date: 23 June 2009

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. Peramivir is predominantly excreted renally. The primary goal of this study was to evaluate the effect of renal impairment (RI) on the pharmacokinetics of peramivir following intravenous administration and to assess the effect of hemodialysis on the pharmacokinetics of peramivir in patients with end-stage renal disease (ESRD).

Trial Objectives
The primary objective of the trial was to:

- evaluate the safety of intravenously administered peramivir in subjects with renal impairment

The secondary objectives of the trial were to:

- evaluate the effect of varying degrees of renal impairment on the pharmacokinetics of intravenously administered peramivir
- evaluate the effect of hemodialysis on the pharmacokinetics of intravenously administered peramivir in patients with end-stage renal disease

Trial Design
This was an open-label study with five cohorts defined by renal function.

Cohort 1	Normal renal function (CL_{CR} >80 mL/min)
Cohort 2	Mild renal impairment (CL_{CR} 50-80 mL/min)
Cohort 3	Moderate renal impairment (CL_{CR} 30-49 mL/min)
Cohort 4	Severe renal impairment (CL_{CR} <30 mL/min)
Cohort 5	End-stage renal disease requiring chronic hemodialysis

Subjects in Cohorts 1-4 received a single dose of intravenous peramivir 2 mg/kg, while subjects in Cohort 5 received single doses of intravenous peramivir 2 mg/kg on two separate occasions: once 2 h before hemodialysis and once at the end of a subsequent hemodialysis. Subjects were confined to the clinic on Day 0 until completion of PK and safety assessments on Day 4 (72 h postdose). Subjects in Cohort 5 were also confined to the clinic from the morning of Day 11 until the morning of Day 15.

Rationale for Dose Selection

The peramivir IV dose of 4 mg/kg was previously found to be reasonably safe in Phase 1 studies; a reduced dose of 2 mg/kg was selected for this renal impairment study based on characterization of peramivir clearance as predominantly renal.

Drug Administration

Peramivir was administered as an IV infusion over 15 minutes, with doses administered in the morning. Subjects were asked to fast (if possible) from 10 h prior to study drug administration until 2 h after study drug administration.

Investigational Product

Peramivir for IV infusion was supplied in 18 mL of a 10 mg/mL stock solution (Lot CT0615) and was to be diluted in 0.9% saline to achieve the appropriate dose in a total volume of 100 mL and infused within 24 h of preparation.

Key Inclusion and Exclusion Criteria

Subjects were healthy males and females at least 18 years of age with a BMI between 19 and 38 kg/m^2 and with normal renal function or a history of stable renal impairment. Females of childbearing potential were surgically sterile, abstinent (from 4 weeks prior to screening through 4 weeks after last dose of study drug), on a stable regimen of hormonal contraceptives for at least 3 months), or using an IUD or a condom with spermicide for at least four weeks. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included renal carcinoma or transplantation within one year prior to Screening, positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

Concomitant medications to treat underlying disease states or medical conditions related to renal insufficiency were permitted.

The following medications and substances were disallowed while subjects were participating in the study:

- live attenuated influenza vaccine (FluMist) from 14 days prior to study drug administration until 10 days post-dose
- live attenuated influenza vaccine (FluMist) at any time during the current influenza season (for subjects 65 years and older)

Sample Collection

For subjects in Cohorts 1-4, blood was collected to assess peramivir concentrations in plasma predose and 0.25 (end of infusion), 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120, 144 and 168 h postdose (after the start of the infusion) on Day 1. Urine was collected predose (-24 to 0 h) and at 0-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h postdose.

For subjects in Cohort 5, blood was collected predose and 0.25 (end of infusion), 1, 2, 3, 6, 9, 12, 24, 36, 48, and 72 h from the same arm to which the infusion was administered on Days 1 and Day 12. Arterial (pre-dialysis) and venous (post-dialysis) samples were also collected 3, 4, 5, and 6 h post-infusion. (Dialysis occurred approximately 2 h post-infusion and lasted for approximately 4 h and Days 1 and 3 [between 48 and 72 h sample collection].) Urine was not collected in Cohort 5.

Analytical Plan

Pharmacokinetic data

Plasma C_{max}, t_{max}, AUC_{last}, AUC_{inf}, terminal $t_{1/2}$, λ_z, V_{ss}, CL, A_e, and extraction ratio (Cohort 5 Dose 1 only) were estimated using standard noncompartmental methods with WinNonlin v.5.0.1 (Pharsight Corp., Mountain View, California) and Sigma Plot (Systat Software Inc., San Jose, California). Urine A_e, f_e, and CL_R were derived from the urine concentrations. Urine and predose plasma samples that were below the limit of quantitation (BLQ) were assigned a value of zero for all analyses.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma and urine samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Methods BTM-BA 030A [plasma] and BTM-BA 033 [urine], Report C06-002-009). Analysis was performed between 27 Nov 2006 and 19 Apr 2007. The first day of sample collection was 23 Oct 2006, so the maximum storage sample time was 178 days, which is within the validated long-term frozen stability duration of 6 months for plasma and urine. The calibration standards ranged from 1-5000 ng/mL (plasma) and 10-50000 (urine) and the quality control (QC) concentrations were 300, 25000, and 45000 ng/mL (plasma) and 30, 2500, 20000, and 40000 ng/mL (urine). All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 30 subjects (six in each cohort) were enrolled in and completed the study. The demographics for each cohort are listed in Table 1.

Table 1. Demographic summary (source: Study Report Table 6)

		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
CL_{CR} (mL/min)	Range	80.7-150.9	56.5-85.9	32.3-43.5	12.7-26.8	requiring dialysis
Age (y)	Mean	52	56.3	56.8	64.0	51.5

	(range)	(41-64)	(44-70)	(28-76)	(54-75)	(37-60)
Male sex	N (%)	4 (66.7)	2 (33.3)	2 (33.3)	3 (50.0)	4 (66.7)
Caucasian	N (%)	4 (66.7)	4 (66.7)	4 (66.7)	2 (33.3)	1 (16.7)
Black/Afr Am	N (%)	1 (16.7)	2 (33.3)	1 (16.7)	4 (66.7)	5 (83.3)
Hispanic	N (%)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Am	N (%)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)

Two subjects (1001 [Cohort 2] and 1002 [Cohort 4]) were excluded from the PK analysis because the infusion durations (55 and 39 minutes, respectively) were longer than the protocol-specified duration of 15 min.

Assessment of plasma peramivir pharmacokinetics

The peramivir concentration-time profiles following a single IV administration of peramivir 2 mg/kg over 15 minutes in subjects with normal renal function; mild, moderate, or severe renal impairment; or end-stage renal disease 2 h before or immediately after hemodialysis are displayed in Figure 1 and pharmacokinetic parameters are listed in Table 2. Note that due to the duration of PK sampling in the ESRD groups, estimation of half-life and dependent parameters (e.g. AUC) may not be reliable.

Figure 1. Mean peramivir plasma concentration-time profiles by renal function group (semilog scale; source: Study Report Figure 1)

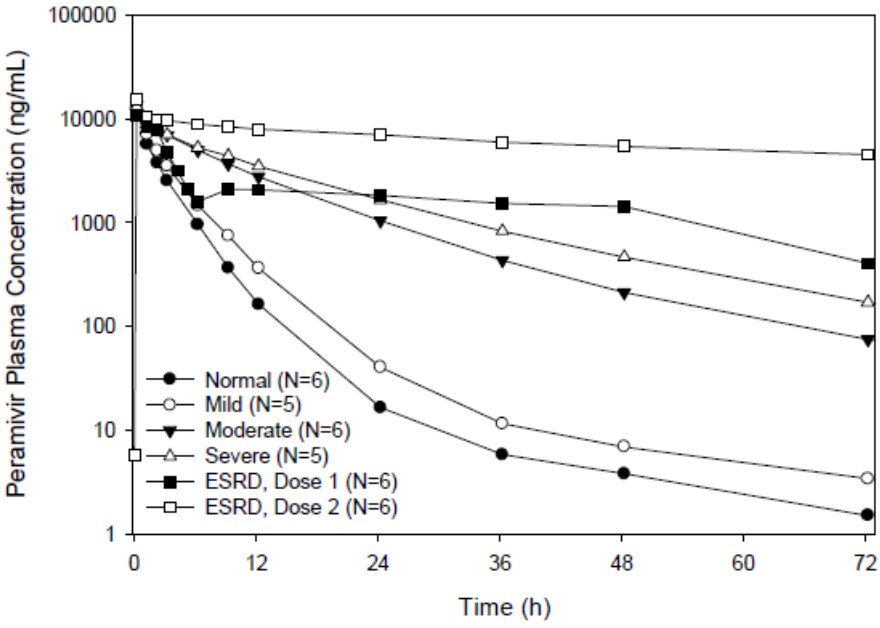


Table 2. Key peramivir pharmacokinetic parameters (source: Study Report Table 9)

Parameter	Renal Function Group					
	Normal (N=6)	Mild (N=5)[4]	Moderate (N=6)	Severe (N=5)[4]	ESRD	
					Dose 1 (N=6)	Dose 2 (N=6)
C_{max} (ng/mL)	12,800 (2,860)	12,500 (3,590)	13,700 (3,780)	13,200 (2,910)	11,000 (3,000)	15,500 (3,610)
T_{max}[1] (h)	0.25 (0.25-0.30)	0.25 (0.23-1.00)	0.25 (0.23-0.32)	0.25 (0.25-0.28)	0.25 (0.25-2.25)	0.25 (0.25-1.25)
$AUC_{0\text{-last}}$ (ng*h/mL)	26,000 (3,200)	33,900 (7,870)	108,000 (31,200)	136,000 (40,600)	107,000[2] (20,300)	470,000[3] (81,200)
$AUC_{0-\infty}$ (ng*h/mL)	26,000 (3,180)	33,900 (7,880)	108,000 (31,200)	137,000 (41,100)	ND	ND
$t_{½}$ (h)	20.7 (4.78)	23.7 (2.84)	28.7 (3.21)	30.7 (2.75)	70.6[2] (33.9)	93.1[3] (53.3)
CL (mL/min)	108 (9.90)	77.9 (21.4)	26.8 (5.35)	21.1 (4.68)	ND	ND
V_{ss} (L)	22.0 (4.35)	20.6 (6.07)	21.9 (3.40)	23.5 (2.80)	ND	ND
CL_{CR} (mL/min)	97.1 (9.23)	66.3 (15.8)	23.2 (5.59)	14.7 (3.27)	ND	ND
f_e (%)	90.4 (7.5)	86.0 (8.5)	85.9 (5.5)	71.6 (16.4)	ND	ND

[1] Presented as Median (Range)
[2] Parameter is truncated to 48 hours post-infusion.
[3] Parameter is truncated to 72 hours post-infusion.
[4] Subjects 1001 (mild renal impairment) and 1002 (severe renal impairment) are excluded as the actual duration of infusion was longer than 15 minutes due to pump malfunction.
ND = not done.
Source: BCX1812-105-PK Report.

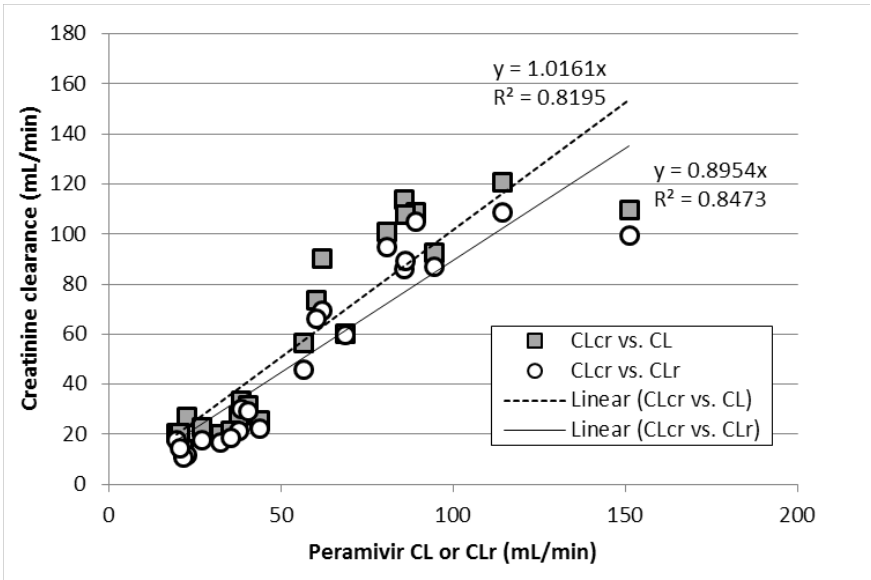
Maximum peramivir concentrations in plasma were reached directly after the infusion in most patients, with comparable mean C_{max} values across renal function groups. Mean AUC values increased with decreasing renal function due to impaired clearance (evident in increasing half-life); this observation was expected based on the characterization of renal clearance as the primary route of elimination in this and other studies (e.g. renal clearance accounted for approximately 90% of total clearance in subjects with normal renal function in this study).

Reviewer's comment: Hemodialysis significantly reduced systemic peramivir exposure in subjects with ESRD by approximately 77%; therefore, peramivir should be administered after hemodialysis.

The correlation between creatinine clearance and peramivir total and renal clearance is shown in Figure 2. Both clearance and renal clearance correlated well with creatinine

clearance. The similarity of the two relationships underscores the primacy of renal clearance in peramivir elimination. The slope of the linear relationship between renal clearance and creatinine clearance was 0.9, suggesting that peramivir is primarily eliminated via glomerular filtration (i.e. active tubular secretion and/or reabsorption do not appear to substantially contribute to peramivir elimination).

Figure 2. Correlation between creatinine clearance and peramivir renal or total clearance (source: Study Report Tables PKT3 and PKT4)



A statistical comparison of peramivir pharmacokinetic parameters is shown in Table 3. After a single dose of IV peramivir, C_{max} was not substantially impacted by renal impairment, but systemic peramivir exposures (AUC) increased with the degree of renal dysfunction (4- and 5-fold increases in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function).

Table 3. Statistical comparison of peramivir plasma pharmacokinetics between renal function groups (source: Study Report Table 5)

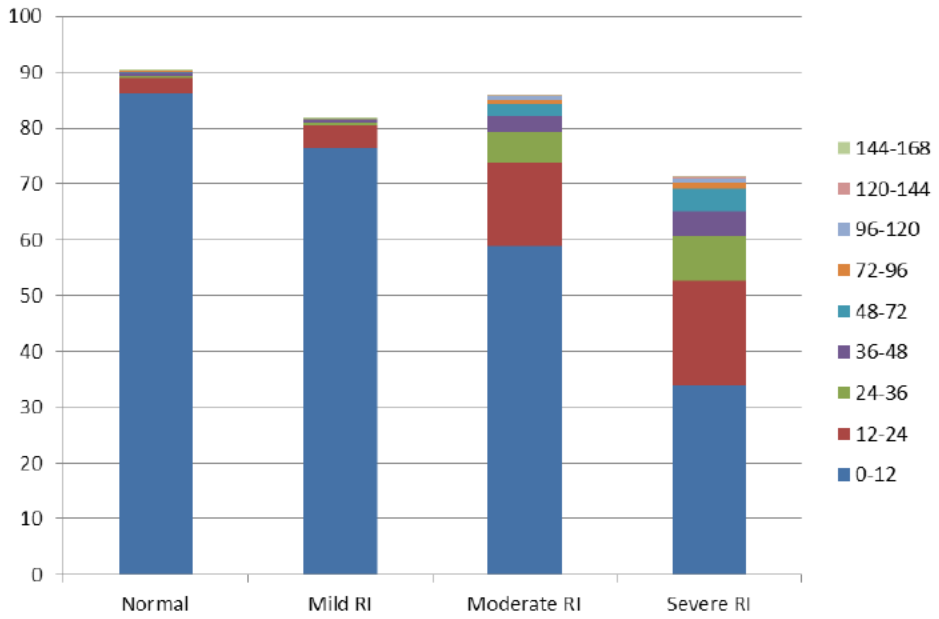
Parameter	Renal Group	N	GLS Mean[1]	Pair	Ratio[2] (%)	90% CI[3] (%)
C_{max} (ng/mL)	Normal	6	12,500			
	Mild	5	12,000	Mild/Normal	96.0	(73.3 – 125.9)
	Moderate	6	13,200	Moderate/Normal	105.6	(81.6 – 136.6)
	Severe	5	12,900	Severe/Normal	103.3	(78.8 – 135.4)
	ESRD, Dose 1	6	10,700	ESRD, Dose1/Normal	85.6	(66.1 – 110.7)
	ESRD, Dose 2	6	15,100	ESRD, Dose2/Normal	120.4	(93.0 – 155.9)
$AUC_{0\text{-last}}$ (ng*h/mL)	Normal	6	25,800			
	Mild	5	33,100	Mild/Normal	128.1	(98.7 – 166.3)
	Moderate	6	104,000	Moderate/Normal	401.6	(313.2 – 514.8)
	Severe	5	131,000	Severe/Normal	508.4	(391.7 – 659.8)
$AUC_{0-\infty}$ (ng*h/mL)	Normal	6	25,900			
	Mild	5	33,100	Mild/Normal	128.0	(98.6 – 166.2)
	Moderate	6	104,000	Moderate/Normal	401.8	(313.3 – 515.2)
	Severe	5	132,000	Severe/Normal	511.7	(394.2 – 664.2)

[1] Geometric least squares mean.
[2] Ratio of GLS means.
[3] 90% confidence interval around the ratio of GLS means
Log transformed PK parameters were fitted on an ANOVA model with cohort as fixed effect.
Subjects 1001 (mild renal impairment) and 1002 (severe renal impairment) are excluded as the actual duration of infusion was longer than 15 minutes due to pump malfunction.
Source: Table PKT5.

Assessment of urine peramivir concentrations

Urinary peramivir was not assessed in patients with ESRD undergoing hemodialysis as it was anticipated that urinary excretion would be minor in these subjects. Analysis of the mean percent of the peramivir dose excreted in urine over time showed that while the majority of the peramivir dose (at least 70%) was excreted over 168 h even in subjects with severe renal impairment, renal clearance was slower in subjects with a greater degree of renal dysfunction (Figure 3).

Figure 3. Mean peramivir f_e (as a percent) by urine collection interval (h postdose) (source: Study Report BCX1812-105-PK Listing PKL3)



Simulation of multiple-dose administration

The Sponsor performed simulations of once- or twice-daily administration of peramivir (dose adjusted for renal function) to patients with renal impairment using a three-compartment model fitted to PK profiles from subjects with normal renal function or mild, moderate, or severe renal impairment in the current study.

Peramivir 600 mg QD for five days was used as the reference treatment in healthy subjects. No dose adjustment was proposed for subjects with mild renal impairment (CL_{CR} ≥50 mL/min) as the observed increase in peramivir AUC (28%) was not considered clinically relevant. Dose reductions (b) (4) were proposed to account for the 4- and 5-fold increases in peramivir AUC in subjects with moderate and severe renal impairment, respectively. Target exposures included a steady-state C_{max} not greater than that observed in subjects with normal renal function, a steady-state AUC_{24} of 100,000 ng.h/mL, and a steady-state C_{trough} of at least 80 ng/mL to ensure sufficient antiviral activity. The proposed reduced doses (b) (4) for patients with moderate and severe renal impairment, respectively) and predicted exposures are listed in Table 4. (b) (4)

Table 4. Predicted steady-state peramivir exposures at proposed doses for multiple dose administration in patients with renal impairment (source: BCX1812-105 PK Study Report Table 7)

Renal Function Group	Proposed Regimen	C_{min} (ng/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
Normal (CL_{CR} > 80 mL/min)	(b) (4)	69.6 392	41,400 21,000	82,800 82,800
Mild (CL_{CR} = 50–80 mL/min)		152 732	41,200 21,200	97,800 97,800
Moderate (CL_{CR} = 30–49 mL/min)		979 1,810	12,500 7,560	80,900 80,800
Severe (CL_{CR} = 10-29 mL/min)		1,340 2,090	9,110 5,960	78,200 78,100
ESRD (Hemodialysis or CL_{CR} < 10 mL/min)		NA[2]	NA[2]	NA[2]

[1] When administered on a dialysis day, peramivir should be administered after hemodialysis.
[2] Exposure parameters are not available because a PK model was not developed in this subject population.
Source: Sections 12.2.2.1 and 12.2.2.2.

Reviewer's comment: At the time of completion of the current study, (b) (4) *The dose proposed in the current NDA submission under review is a single administration of peramivir 600 mg.*

Assessment of peramivir protein binding

The extent of plasma protein binding was evaluated in plasma samples collected predose, to which peramivir was added to final concentrations of 4.5, 45, and 4500 ng/mL (for reference, the mean C_{max} in subjects with normal renal function was 12,800 ng/mL). Peramivir plasma protein binding was low in all renal function groups (range: 0-4.9%) and independent of peramivir concentration and renal function.

Results of safety analysis

There were seven treatment-emergent adverse events reported during the study that were categorized as possibly (diarrhea, nasopharyngitis, gout, pain in extremity, headache) or probably (facial neuralgia, somnolence) related to study treatment; all were mild or moderate in severity. There was no relationship between degree of renal impairment and incidence of TEAE. No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of peramivir following a single intravenous administration of 2 mg/kg IV peramivir were evaluated in subjects with normal renal function; mild, moderate, or severe renal impairment; or ESRD before or after dialysis. While C_{max} was not substantially affect by renal dysfunction, the mean peramivir AUC_{inf} values were approximately 1.3-, 4.0, and 5.1-fold higher compared to subjects with normal renal function; with increasing renal dysfunction there was a corresponding decrease in clearance. Because of the increases in systemic peramivir exposures and the

likelihood of accumulation after multiple dosing in patients with moderate or severe renal impairment, (b) (4) Due to logistical constraints on PK sampling times in subjects undergoing hemodialysis, accurate systemic exposures (AUC) could not be estimated; however, available data indicate that hemodialysis removes peramivir from systemic circulation, so peramivir should be administered post-hemodialysis in subjects with ESRD. IV administration of peramivir was generally well-tolerated. All treatment-emergent adverse events that were considered possibly or probably related to peramivir were mild or moderate in severity and no subjects discontinued peramivir due to adverse events.

Trial BCX1812-109
A Randomized, Open-Label, 3-Period Crossover Drug Interaction Study of Oral Oseltamivir with Intravenous Peramivir in Healthy Volunteers

Trial Period
13 Nov 2009 to 15 Dec 2009
Final report date: 16 Aug 2010

Trial Site
(b) (4)

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. Oseltamivir, a prodrug of oseltamivir carboxylate, is a neuraminidase inhibitor approved for the prophylaxis and treatment of influenza. Oseltamivir is extensively metabolized by hepatic esterases to form oseltamivir carboxylate, which is eliminated renally. The primary goal of this study was to evaluate the potential for a PK interaction between two drugs that may be used concurrently in patients with influenza infection.

Trial Objectives
The primary objective of the trial was to:

- assess potential PK interactions when single doses of oseltamivir and peramivir are coadministered

The secondary objectives of the trial were to:

- evaluate the safety and tolerability of peramivir when coadministered with oseltamivir compared with administration of peramivir alone and rimantadine alone in healthy volunteers

Trial Design
This was a randomized, open-label, three-period, three-sequence crossover study. The three treatments were:

Treatment 1: Peramivir IV 600 mg
Treatment 2: Oseltamivir PO 75 mg
Treatment 3: Peramivir IV 600 mg with oseltamivir PO 75 mg

Seven healthy volunteers were randomized to each sequence (1-2-3, 3-1-2, 2-3-1). Subjects were confined to the clinic on Day 0 until completion of the 24 h PK and safety assessments for each period. There was a seven day washout period between treatments.

Rationale for Dose Selection

The peramivir IV dose of 600 mg is being evaluated in safety and efficacy trials. The oseltamivir dose of 75 mg is equal to the daily dose recommended for prophylaxis and half of the daily dose recommended for treatment (75 mg BID). Because no PK interaction was anticipated, a single dose study was considered appropriate.

Drug Administration

Subjects received study drug(s) following a standard light breakfast. Peramivir was administered as an IV infusion over 15 minutes. Oral oseltamivir was administered by study staff.

Investigational Product

Peramivir for IV infusion was supplied in 20 mL of a 10 mg/mL stock solution (Lot 7439). Oseltamivir 75 mg was a capsule containing pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate as inactive ingredients (Lot U2080-01).

Key Inclusion and Exclusion Criteria

Subjects were nonsmoking healthy males and females between 18 and 60 years of age with a BMI between 19 and 35 kg/m^2 and with normal renal (creatinine clearance of at least 80 mL/min). Females of childbearing potential were surgically sterile, abstinent (from 4 weeks prior to screening through 4 weeks after last dose of study drug), on a stable regimen of hormonal contraceptives for at least 3 months), or using an IUD or a condom with spermicide for at least four weeks. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included history of clinically significant syncope or arrhythmias, abnormal ECG, history or evidence of drug or alcohol abuse, or chronic illness requiring ongoing use of medications during the study.

Concomitant Medications

Concomitant medications, including prescription drugs (with the exception of hormonal contraceptives) and herbal and mineral remedies, were prohibited during the study.

Sample Collection

For subjects receiving peramivir alone or peramivir with oseltamivir, blood was collected predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72 h postdose. For subjects receiving oseltamivir alone, blood was collected predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 48 h postdose.

Analytical Plan

Pharmacokinetic data

Plasma C_{max}, t_{max}, AUC_{last}, AUC_{inf}, terminal $t_{1/2}$, λ_z, V_{ss}, and CL were estimated using standard noncompartmental methods with WinNonlin v.6.0 (Pharsight Corp., Mountain View, California), SAS (SAS Institute, Inc., Cary, North Carolina), and Sigma Plot (Systat Software Inc., San Jose, California). Predose samples (and any other samples that

preceded quantifiable samples) that were below the lower limit of quantitation (BLQ) were assigned a value of zero. Following t_{max}, BLQ values were treated as missing. A mixed effects repeated measures ANOVA with fixed effects for treatment, period, and sequence and a random effect for subject within sequence was used to compare treatments (LSMeans and 90% CI). A no-effect margin of 80-125% was used.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma samples were measured by LC-MS/MS by BioCryst Pharmaceuticals, Inc. (Birmingham, Alabama, USA; Method BTM-BA 030A, Report BCX1812-109-BA). Analysis was performed between 19 Jan and 16 Feb 2010. The first day of sample collection was 24 Nov 2009, so the maximum storage sample time was 53 days, which is within the validated long-term frozen stability duration of 6 months for plasma. The calibration standards ranged from 2.5-5000 ng/mL and the quality control (QC) concentrations were 7.5, 250, 2000, and 4000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Concentrations of oseltamivir and oseltamivir carboxylate in plasma samples were measured by LC-MS/MS by (b) (4) Method BASi SAP.1354, Report 0527-09386-001). Analysis was performed between 18 Jan and 1 Feb 2010. The first day of sample collection was 24 Nov 2009, so the maximum storage sample time was 38 days, which is within the validated long-term frozen stability duration of 346 days. The calibration standards ranged from 1-250 and 10-10000 ng/mL for oseltamivir and oseltamivir carboxylate, respectively, and the quality control (QC) concentrations were 3.1, 100, and 200 ng/mL for oseltamivir and 30.0, 4000, and 8000 ng/mL for oseltamivir carboxylate. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

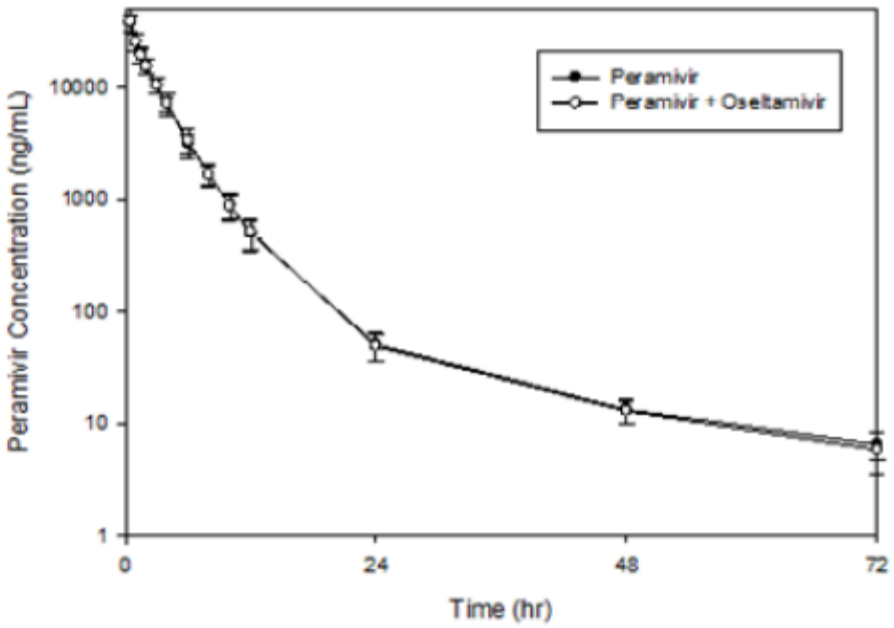
Trial population

A total of 21 healthy adults between the ages of 33 and 58 were randomized and received study treatment; all completed the study. Slightly more than half of the subjects were female (52%) and all were Caucasian (100%).

Assessment of plasma peramivir pharmacokinetics

The mean peramivir concentration-time profiles following a single IV administration of peramivir 600 mg over 15 minutes with or without oral oseltamivir 75 mg are displayed in Figure 1 and pharmacokinetic parameters are listed in Table 1. Peramivir PK was similar regardless of oseltamivir coadministration and was comparable to historical data. Statistical comparisons indicated that peramivir PK was unchanged in the presence of oseltamivir (GMR for AUC: 101.3% with 90% CI of 98.8-103.9%, Table 2).

Figure 1. Mean peramivir plasma concentration-time profiles with oseltamivir (open circles) or alone (closed circles) (semilog scale; source: Study Report Figure 3)



Source: BCX1812-109-PK

Table 1. Key peramivir pharmacokinetic parameters (source: Study Report Table 6)

Parameter	Treatment Group Mean (SD)	
	IV Peramivir 600 mg (N=21)	*Oral Oseltamivir 75 mg + IV Peramivir 600 mg (N=21)*
C_{max} (ng/mL)	37230 (7045)	38470 (6273)
T_{max}[1] (h)	0.50 (0.50, 0.53)	0.50 (0.50, 0.55)
AUC_{0-last} (ng*hr/mL)	89230 (12950)	90380 (12580)
$AUC_{0-\infty}$ (ng*hr/mL)	89380 (12990)	90530 (12620)
Cl (mL/hr)	6854 (1024)	6762 (1019)

[1] T_{max} is reported as median (range)
Source: Table 14.4.7.

Table 2. Statistical comparison of peramivir, oseltamivir carboxylate, and oseltamivir exposures following administration of peramivir and oseltamivir in combination or separately (source: Study Report Table 9)

	Peramivir	Oseltamivir	Oseltamivir Carboxylate
C_{max} (ng/mL)[1, 2, 3]	103.8% (99.9%, 107.8%)*	120.0% (99.9%, 144.0%)%)	101.3% (96.7%, 106.1%)*
$AUC_{0\text{-last}}$ (ng*hr/mL)[1, 2, 3]	101.3% (98.8%, 103.9%)*	101.7% (96.9%, 106.8%)*	100.0% (97.4%, 102.6%)*
$AUC_{0\text{-inf}}$ (ng*hr/mL)[1,2, 3]	101.3% (98.8%, 103.9%)*	102.2% (97.4%, 107.2%)*	100.9% (98.8%, 103.1%)*

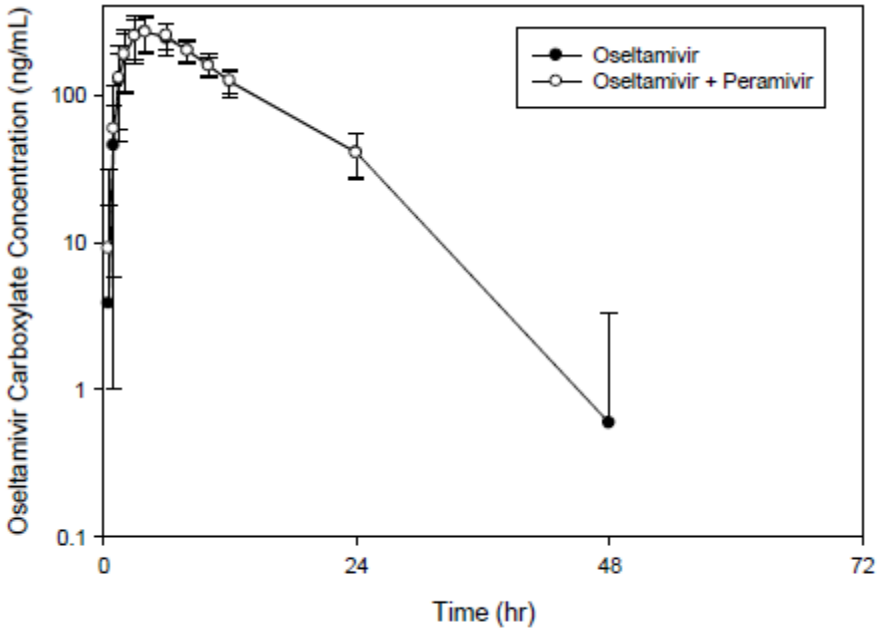
1 The least square means and confidence intervals are based on an ANOVA model of the natural log transformed parameter.
2. C_{max} and AUC ratios of the geometric means and confidence intervals for peramivir and oseltamivir in combination compared with monotherapy
3. The least square means and confidence 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).
Note: A * indicates that the 90% confidence interval falls entirely within the interval (80.00%, 125.00%), indicating that there is no drug-drug interaction.

Source: Table 14.4.7.

Assessment of plasma oseltamivir carboxylate pharmacokinetics

The mean oseltamivir carboxylate concentration-time profiles following a single oral dose of oseltamivir 75 mg with or without peramivir IV 600 mg are displayed in Figure 2 and pharmacokinetic parameters are listed in Table 3. Oseltamivir carboxylate PK was similar regardless of peramivir coadministration. Statistical comparisons indicated that oseltamivir carboxylate PK was unchanged in the presence of peramivir (GMR for AUC: 100.0% with 90% CI of 97.4-102.6%, Table 2).

Figure 2. Mean oseltamivir carboxylate plasma concentration-time profiles following administration of oseltamivir with peramivir (open circles) or alone (closed circles) (semilog scale; source: Study Report Figure 4)



Source: BCX1812-109-PK

Table 3. Key oseltamivir carboxylate pharmacokinetic parameters (source: Study Report Table 7)

Parameter	Treatment Group Mean (SD)	
	Oral Oseltamivir 75 mg (N=21)	*Oral Oseltamivir 75 mg + IV Peramivir 600 mg (N=21)*
C_{max} (ng/mL)	283 (76.4)	284 (60.4)
T_{max}[1] (h)	4.00 (3.00, 8.00)	4.00 (3.00, 6.00)
$AUC_{0\text{-last}}$ (ng*hr/mL)	3260 (643)	3240 (543)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	3670 (700)	3690 (617)

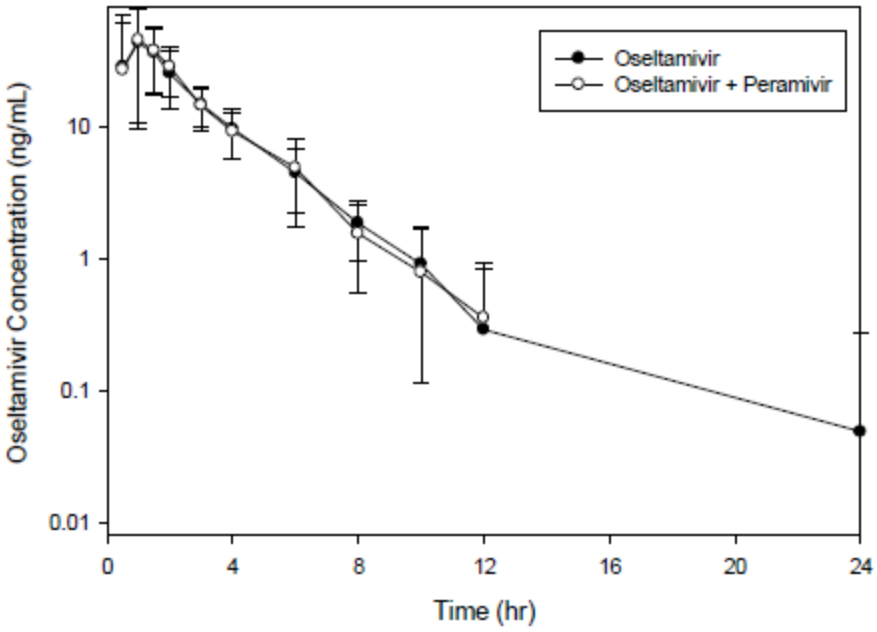
[1] T_{max} is reported as median (range)
Source: Table 14.4.7.

Assessment of plasma oseltamivir pharmacokinetics

The mean oseltamivir concentration-time profiles following a single oral dose of oseltamivir 75 mg with or without peramivir IV 600 mg are displayed in Figure 3 and pharmacokinetic parameters are listed in Table 4. Overall, oseltamivir PK was comparable between treatments. Statistical comparisons indicated that oseltamivir AUC was statistically unchanged in the presence of peramivir (GMR: 101.7% with 90% CI of 96.9-106.8%, Table 2). Oseltamivir Cmax was statistically significantly higher in the

presence of peramivir compared to administration alone (GMR: 120.0% with 90% CI of 99.9-144.0%, Table 2). However, it should be noted that oseltamivir plasma concentrations are low due to its rapid conversion to oseltamivir carboxylate; additionally, the study was not powered to assess differences in oseltamivir PK.

Figure 3. Mean oseltamivir plasma concentration-time profiles with peramivir (open circles) or alone (closed circles) (semilog scale; source: Study Report Figure 5)



Source: BCX1812-109-PK

Table 4. Key oseltamivir parameters (source: Study Report Table 7)

Parameter	Treatment Group Mean (SD)	
	Oral Oseltamivir 75 mg (N=21)	*Oral Oseltamivir 75 mg + IV Peramivir 600 mg (N=21)*
C_{max} (ng/mL)	60.4 (41.7)	65.6 (28.5)
T_{max}[1] (h)	1.00 (0.50, 3.00)	1.00 (0.50, 2.00)
AUC_{0-last} (ng*hr/mL)	115 (29.6)	117 (27.3)
$AUC_{0-\infty}$ (ng*hr/mL)	119 (29.9)	122 (27.0)
Cl/F (mL/hr)	671000 (192000)	656000 (194000)

[1] T_{max} is reported as median (range)
Source: Table 14.4.7.

Trial Summary

In this study, the pharmacokinetics of peramivir, oseltamivir, and oseltamivir carboxylate were evaluated following a single intravenous administration of 600 mg peramivir, a single oral dose of oseltamivir 75 mg, or peramivir and oseltamivir concurrently. The results of the study suggest that no there were no statistically significant alterations in peramivir or oseltamivir carboxylate PK upon coadministration. This result was not unexpected: both oseltamivir carboxylate and peramivir are renally excreted, but the excretion capacity of the renal pathway is large and a PK interaction between peramivir and oseltamivir carboxylate is unlikely to be caused by this mechanism. A slight but statistically significant increase (20%) in oseltamivir C_{max} was observed in the presence of peramivir; however, the study was not powered to assess changes in oseltamivir PK and the small difference is not clinically relevant. Overall, peramivir IV and oral oseltamivir were generally well-tolerated regardless of whether they were administered separately or in combination.

Trial BCX1812-110
A Blinded Drug-Drug Interaction Study to Assess the Effect of Intravenous Peramivir on the Pharmacokinetics of an Oral Contraceptive Containing Ethinyl Estradiol and Levonorgestrel in Healthy Female Volunteers

Trial Period
19 Jun 2011 to 5 Jan 2012
Final report date: 8 Aug 2013

Trial Site
ICON Development Solutions, San Antonio, Texas, USA

Trial Rationale
Peramivir (BCX1812) is an inhibitor of influenza neuraminidase currently under development for the treatment of influenza A and B infection. In clinical practice, the likelihood of concurrent of use peramivir with an oral contraceptive is high because peramivir may be administered while a patient is taking an oral contraceptive. The metabolism of oral contraceptives has not been fully elucidated. The primary goal of this study was to evaluate the potential for a PK interaction between peramivir and levonorgestrel/ethinyl estradiol, a representative oral contraceptive.

Trial Objectives
The primary objective of the trial was to:

- assess PK of levonorgestrel and ethinyl estradiol alone compared with coadministration with a single dose of peramivir in healthy female volunteers

The secondary objectives of the trial were to:

- evaluate the safety and tolerability of levonorgestrel and ethinyl estradiol alone compared with coadministration with a single dose of peramivir in healthy female volunteers

Trial Design
This was a randomized, blinded, placebo-controlled, two-treatment, two-period, two-sequence crossover study. The two treatments were:

Treatment 1: Levonorgestrel/ethinyl estradiol PO 0.15/0.3 mg QD with placebo
Treatment 2: Levonorgestrel/ethinyl estradiol PO 0.15/0.3 mg QD with peramivir IV 600 mg

Levonorgestrel/ethinyl estradiol (LEVORA® 0.15/30-28) was administered for 21 days (Days 1-20) and a placebo pill was administered for seven days (Days 21-28). Treatment

Period 1 occurred at any time during Days 6-13 (to allow levonorgestrel and ethinyl estradiol to reach steady-state) and Treatment Period 2 occurred at any time during Days 14-20. During each Treatment Period, a single dose of peramivir IV or placebo IV was administered.

Thirty healthy female volunteers were randomized to one of two sequences (1-2, 2-1). Subjects were confined to the clinic on Day 0 until completion of the 24 h PK and safety assessments for each Treatment Period.

Rationale for Dose Selection

The peramivir IV dose of 600 mg is being evaluated in safety and efficacy trials. The levonorgestrel/ethinyl estradiol dose of 0.15/0.03 mg QD is equal to the daily dose recommended for effective contraception.

Drug Administration

On PK sampling days, subjects received study drug(s) in the fasted state. Peramivir was administered as an IV infusion over 15 minutes. Oral levonorgestrel/ethinyl estradiol was administered by study staff during the Treatment Periods and self-administered during all other study periods.

Investigational Product

Peramivir for IV infusion was supplied in 20 mL of a 10 mg/mL stock solution. Commercially available LEVORA® 0.15/30-28 was supplied as 21 levonorgestrel/ethinyl estradiol 0.15/0.03 mg tablets and seven placebo tablets in a 28-tablet dispenser. No Lot or Batch information was provided for either product.

Key Inclusion and Exclusion Criteria

Subjects were nonsmoking healthy females between 18 and 40 years of age with a BMI between 19 and 32 kg/m^2 and with normal renal (creatinine clearance of at least 80 mL/min). Subjects had been receiving a 28-day oral contraceptive regimen for at least one month. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included any chronic or medically uncontrolled condition or important medical history, history of clinically significant syncope or arrhythmias, abnormal ECG, history or evidence of drug or alcohol abuse, or chronic illness requiring ongoing use of medications during the study.

Concomitant Medications

Concomitant medications, including prescription drugs (with the exception of hormonal contraceptives) and herbal and mineral remedies, were prohibited during the study.

Sample Collection

Blood was collected for analysis of peramivir, levonorgestrel, and ethinyul estradiol predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h postdose during Treatment Periods 1 and 2.

Analytical Plan

Pharmacokinetic data

Plasma C_{max}, t_{max}, AUC_{last}, AUC_{inf}, terminal $t_{1/2}$, λ_z, V_{ss}, and CL were estimated using standard noncompartmental methods with WinNonlin v.6.0 (Pharsight Corp., Mountain View, California), SAS (SAS Institute, Inc., Cary, North Carolina), and Sigma Plot (Systat Software Inc., San Jose, California). Predose samples (and any other samples that preceded quantifiable samples) that were below the lower limit of quantitation (BLQ) were assigned a value of zero. Following t_{max}, BLQ values were treated as missing. A mixed effects repeated measures ANOVA with fixed effects for treatment, period, and sequence and a random effect for subject within sequence was used to compare treatments (LSMeans and 90% CI). A no-effect margin of 80-125% was used.

Due to a misinterpretation of the protocol by the CRO, predose and 24 h sample collections occurred following the subsequent levonorgestrel/ethinyl estradiol administration; therefore, concentrations at these timepoints were estimated by linear regression and extrapolation from data in the terminal portion of the concentration-time curve. The primary endpoint of AUC_{0-24h} was modified to AUC calculated using a 0.5 h start time based on the available observed data. Comparisons of the primary endpoint and AUC calculated using extrapolation suggested that this protocol deviation did not substantially alter PK results.

Trial Results

Bioanalytical methods

Concentrations of peramivir in plasma samples were measured by LC-MS/MS by [redacted] (b) (4) Method BTM-BA 030A, Report BAR-BCX1812-110). Analysis was performed between 30 Jan and 18 May 2012. The first day of sample collection was 28 Jun 2011, so the maximum storage sample time may have exceeded the validated long-term frozen stability duration of 6 months for plasma; this potential deviation is acceptable because the PK data are not included in the proposed labeling. The calibration standards ranged from 2.5-5000 ng/mL and the quality control (QC) concentrations were 7.5, 250, 2000, and 4000 ng/mL. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Concentrations of levonorgestrel and ethinyl estradiol in plasma samples were measured by LC-MS/MS by [redacted] (b) (4) Method 1003-07-1078-01). The lower limit of quantitation was 5 pg/mL and 100 pg/mL for ethinyl estradiol and levonorgestrel, respectively.

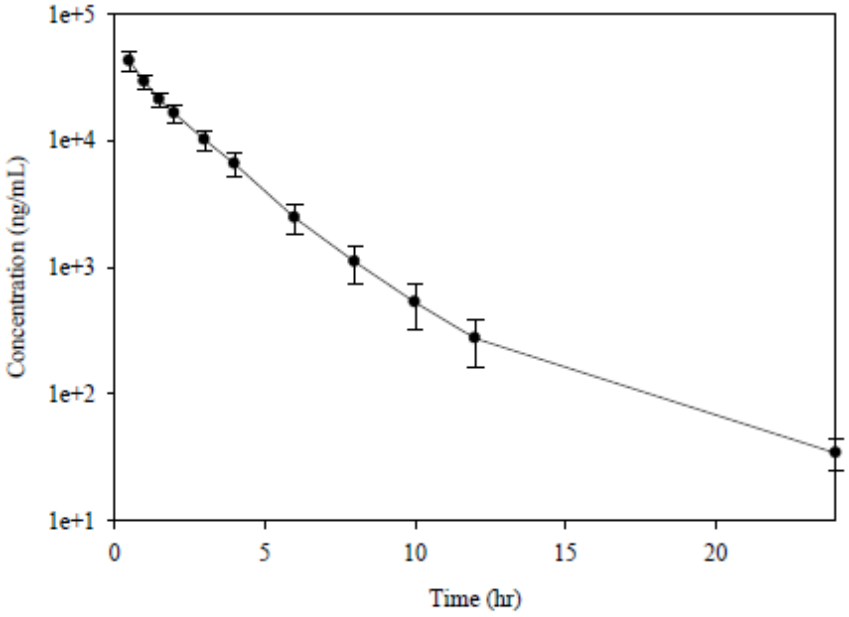
Trial population

A total of 34 healthy females between the ages of 18 and 40 were randomized (17 to each sequence). Thirty subjects received at least one dose of study drug and all but four completed the study (two withdrew after completion of PK assessments). Three subjects who discontinued early withdrew consent and one was discontinued by the Investigator due to non-compliance. The majority of subjects were Caucasian (77%).

Assessment of plasma peramivir pharmacokinetics

The mean peramivir concentration-time profiles following a single IV administration of peramivir 600 mg over 15 minutes with or without oral levonorgestrel/ethinyl estradiol 0.15/0.30 mg are displayed in Figure 1 and pharmacokinetic parameters are listed in Table 1. Although peramivir was not administered alone in this study, comparisons to historical data suggest that peramivir PK was similar regardless of levonorgestrel/ethinyl estradiol coadministration (Table 1).

Figure 1. Mean peramivir plasma concentration-time profiles with levonorgestrel/ethinyl estradiol (open circles) or alone (closed circles) (semilog scale; source: Study Report Figure 5)



All subjects plotted.
Source: BCX1812-110-PK Report

Table 1. Cross-study comparison of peramivir pharmacokinetic parameters (source: Study Report Table 12)

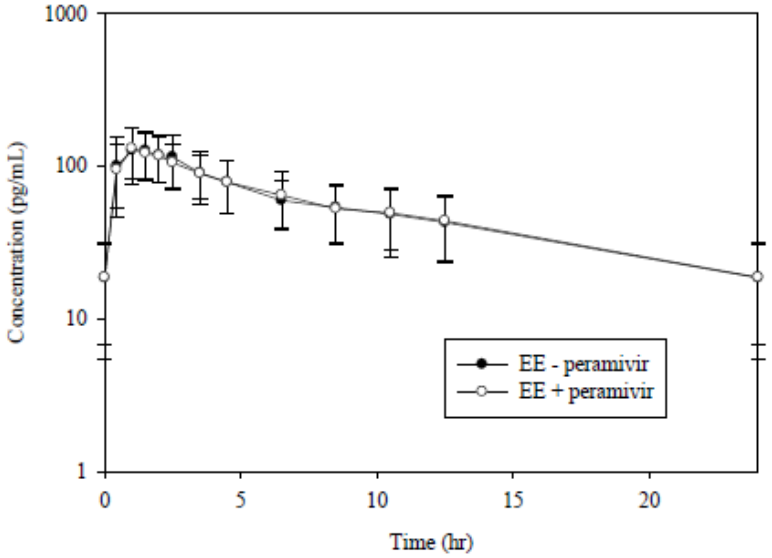
	Peramivir + Ethinyl Estradiol/Levonorgestrel (N=28)	IV Placebo Study BCX1812-108 (N=20)
AUC_{0-24} (hr*ng/mL)		
N	28	20
Mean (SD)	86840 (12470)	80230 (12450)
Geometric Mean	86000	79280
Median	87850	79630
Min, Max	65940, 122700	51840, 104400
Coefficient of Variation	14.36	15.52
C_{max} (ng/mL)		
N	28	20
Mean (SD)	42500 (7140)	37680 (7819)
Geometric Mean	42000	36940
Median	41700	35900
Min, Max	29700, 67400	24400, 56300
Coefficient of Variation	16.8	20.76
T_{max} (hr)		
N	28	20
Mean (SD)	0.51 (0.026)	0.50 (0.00)
Median	0.50	0.50
Min, Max	0.50, 0.62	0.50, 0.50
Coefficient of Variation	5.2	0.00

Source: BCX1812-110 Data Listing 12.2 and Table 11.2
BCX1812-108 Clinical Study Report

Assessment of plasma ethinyl estradiol pharmacokinetics

The mean ethinyl estradiol concentration-time profiles following at least seven days of levonorgestrel/ethinyl estradiol 0.15/0.03 mg QD with peramivir IV 600 mg or placebo IV are displayed in Figure 2 and a comparison of AUC are listed in Table 2. Ethinyl estradiol PK was similar regardless of peramivir coadministration. Statistical comparisons indicated that ethinyl estradiol PK was unchanged in the presence of peramivir (GMR for AUC: 97.9% with 90% CI of 90.5-106.3%, Table 2).

Figure 2. Mean ethinyl estradiol plasma concentration-time profiles following administration with peramivir (open circles) or alone (closed circles) (semilog scale; source: Study Report Figure 3)



* Extrapolated 24-hour concentrations are used for the predose and 24-hour postdose concentrations
All subjects are plotted here independent of day of sampling or sequence of peramivir/placebo dosing
Source: BCX1812-110-PK Report

Table 2. Ethinyl estradiol AUC comparisons (source: Study Report Table 6)

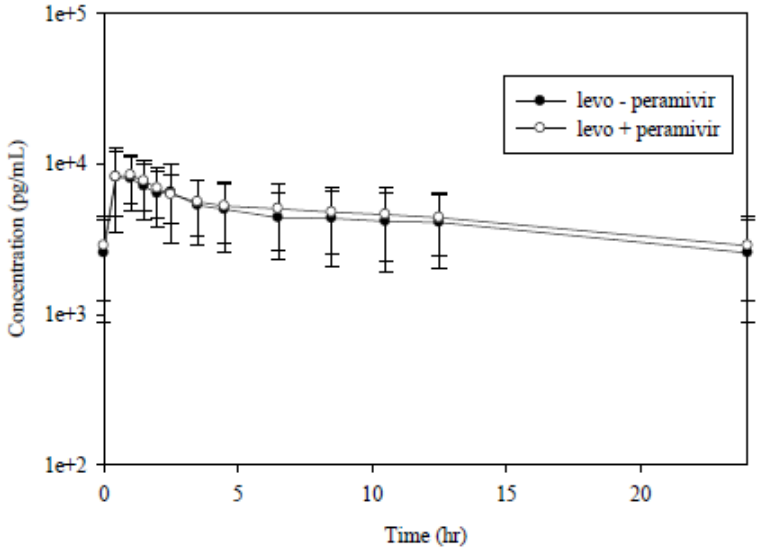
	Peramivir + Ethinyl Estradiol (N=28)	Placebo + Ethinyl Estradiol (N=28)
$AUC_{0.5-12}$ (hr*pg/mL)		
N	28	27
Mean (SD)	875.2 (312.5)	869.8 (309.8)
Geometric Mean	822.9	821.0
Median	873.5	784.2
Min, Max	356.4, 1777	394.5, 1588
Coefficient of Variation	35.71	35.62
Least Square Means (Standard Error)	821.0 (1.068)	838.7 (1.068)
Ratio of Geometric Means of IV Peramivir + Ethinyl Estradiol to Ethinyl Estradiol	97.9 %	
(90% CI) [1]	(90.5%, 106.3%)*	
$AUC_{0.5-24}$ (hr*pg/mL)		
N	28	27
Mean (SD)	1212 (477.6)	1200 (474.2)
Geometric Mean	1129	1119
Median	1204	1103
Min, Max	503.5, 2754	538.2, 2384
Coefficient of Variation	39.42	39.54
Least Square Means (Standard Error)	1122 (1.073)	1144 (1.074)
Ratio of Geometric Means of IV Peramivir + Ethinyl Estradiol to Ethinyl Estradiol	98.1 %	
(90% CI) [1]	(90.5%, 106.3%)*	

Note: The geometric least square means and confidence intervals are based on an ANOVA model of the natural log transformed parameter.
[1] A * indicates that the 90% CI falls entirely within the interval (80.00%, 125.00%), indicating that there is no DDI.
Source: Listing 12.2 and Table 11.2.

Assessment of plasma levonorgestrel pharmacokinetics

The mean levonorgestrel concentration-time profiles following at least seven days of levonorgestrel/ethinyl estradiol 0.15/0.03 mg QD with peramivir IV 600 mg or placebo IV are displayed in Figure 3 and a comparison of AUC are listed in Table 3. Levonorgestrel PK was similar regardless of peramivir coadministration. Statistical comparisons indicated that levonorgestrel PK was unchanged in the presence of peramivir (GMR for AUC: 105.6% with 90% CI of 99.4-112.1%, Table 3).

Figure 3. Mean levonorgestrel plasma concentration-time profiles with peramivir (open circles) or alone (closed circles) (semilog scale; source: Study Report Figure 4)



* Extrapolated 24-hour concentrations are used for the pre-dose and 24-hour postdose concentrations. All subjects are plotted here independent of day of sampling or sequence of peramivir/placebo dosing.
Source: BCX1812-110-PK Report

Table 3. Levonorgestrel AUC comparisons (source: Study Report Table 9)

	Peramivir + Levonorgestrel l (N=28)	Placebo + Levonorgestrel (N=28)
$AUC_{0.5-12}$ (hr*pg/mL)		
N	26	26
Mean (SD)	64640 (28800)	59480 (28810)
Geometric Mean	59420	54540
Median	54160	51570
Min, Max	29950, 155900	31490, 163000
Coefficient of Variation	44.55	48.44
Least Square Means (Standard Error)	58720 (1.079)	55900 (1.080)
Ratio of Geometric Means of IV Peramivir + Levonorgestrel to Levonorgestrel	105.0 %	
(90% CI) [1]	(99.4%, 111.0%)*	
$AUC_{0.5-24}$ (hr*pg/mL)		
N	26	26
Mean (SD)	105400 (49640)	96460 (49900)
Geometric Mean	95770	87420
Median	89480	85220
Min, Max	45390, 261800	44480, 282200
Coefficient of Variation	47.11	51.73
Least Square Means (Standard Error)	94430 (1.085)	89460 (1.085)
Ratio of Geometric Means of IV Peramivir + Levonorgestrel to Levonorgestrel	105.6 %	

(90% CI) [1]	(99.4%, 112.1%)*	
AUC_{0-24} (hr*pg/mL)		
N	26	26
Mean (SD)	107900 (50620)	98940 (51490)
Geometric Mean	98120	89610
Median	91660	87160
Min, Max	46850, 267600	46040, 291300
Coefficient of Variation	46.92	52.04
Least Square Means (Standard Error)	96700 (1.085)	91680 (1.085)
Ratio of geometric means of IV Peramivir + Levonorgestrel to Levonorgestrel	105.5 %	
(90% CI) [1]	(99.4%, 111.9%)*	

Note: The geometric least square means and CIs are based on an ANOVA model of the natural log transformed parameter. [1] A * indicates that the 90% CI falls entirely within the interval (80.00%, 125.00%), indicating that there is no DDI.
Data Source: Table 11.2.

Trial Summary

In this study, the pharmacokinetics of peramivir, levonorgestrel, and ethinyl estrdiol were evaluated following multiple doses of levonorgestrel/ethinyl estradiol 0.15/0.03 mg QD and a single intravenous administration of 600 mg peramivir or placebo. The results of the study suggest that no there were no significant alterations in levonorgestrel or ethinyl estradiol PK upon coadministration with peramivir, and comparison to historical data suggest that peramivir PK was unchanged by concurrent use of levonorgestrel/ethinyl estradiol 0.15/0.03 mg QD. Overall, peramivir IV and the representative oral contraceptive levonorgestrel/ethinyl estradiol were generally well-tolerated.

In vitro studies

1. Distribution

- DM99305: Peramivir plasma protein binding
- DM99362: Peramivir plasma protein binding and RBC partitioning

Summary: Plasma protein binding of peramivir was low in humans (<18%). Peramivir did not partition into red blood cells.

2. Metabolism and elimination

- DM98357: In vitro metabolism in S9 fractions

Summary: Peramivir is not extensively metabolized in rat, dog, or human hepatic S9 fractions (>95% detected unchanged). Only one metabolite, M1, was detected in rat and human S9 fractions but not in dog. This metabolite was formed from oxidation of the cyclopentyl ring.

3. Drug interaction potential

- 7SHIOP: P-gp transport of and inhibition by peramivir in Caco-2 cells
- DM01372: Transport characteristics of peramivir
- DM98399: Inhibition of CYP isoforms
- DM99339: Induction of CYP isoforms
- DM99401: Interaction with acetaminophen

Summary: Peramivir was neither a substrate nor an inhibitor of P-gp. No major transporter-mediated drug interactions are anticipated. Peramivir did not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at concentrations up to 100 uM, nor did it induce activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP3D6, CYP2E1, or CYP3A4 at concentrations up to 10 uM. In addition, peramivir did not substantially influence glucuronidation of APAP at concentrations up to 10 uM. Based on these studies, peramivir has a low potential to perpetrate or be a victim of drug-drug interactions.

DM99305: Binding of RWF-270201-162 to the proteins of male and female human plasma

Introduction
In this study, the binding of peramivir to human plasma proteins over a therapeutic concentration range was evaluated using equilibrium dialysis.

Materials and Methods
Peramivir was added to pooled plasma from healthy volunteers (separated by gender) to final concentrations of 1, 5, 10, 50, 100, 500, and 1000 ng/mL. Equilibrium dialysis with Sorenson's buffer was conducted at 37ºC for 4 hours. Samples were analyzed using LC-MS/MS.

Results
Less than 30% of peramivir was protein-bound in human plasma (Table 1). The extent of plasma protein binding did not appear to be highly correlated with peramivir concentration but appeared to be slightly higher in males compared to females. These minor differences in plasma protein binding are not expected to be clinically relevant.

Table 1: Peramivir protein binding in human plasma (source: Study Report Table SD3)

Gender		Spiked Plasma Concentration (ng/mL)						
		1	5	10	50	100	500	1000
Male	Mean	-55.29	17.45	20.67	14.72	25.46	28.56	26.03
	SD	35.05	9.78	11.19	6.33	7.05	4.07	4.35
Female	Mean	-38.39	-4.26	-5.92	4.49	8.20	11.99	12.32
	SD	22.13	18.04	14.28	8.06	8.98	3.05	7.39

[a] % bound = 100 − [100 × (conc of buffer/conc of plasma)]

Conclusion
The extent of peramivir binding to human plasma proteins was low (<30%) in plasma samples from both healthy male and female subjects.

DM99362: Determination of protein binding and red blood cell partitioning of ^{14}C-RWJ-270201 in mouse, rat, rabbit, dog, monkey, and human

Introduction
In this study, the protein binding of peramivir in CD-1 mouse, Sprague-Dawley rat, New Zealand white rabbit, beagle dog, cynomolgus monkey, and human plasma was evaluated using equilibrium dialysis.

Materials and Methods
Peramivir was added to pooled plasma from at least three males and three females from each species (rat, dog, mouse, monkey, and human) to final concentrations over the range of 10-1000 ng/mL. Equilibrium dialysis with phosphate buffer was conducted at 37ºC for 4 hours. Samples were analyzed for radioactivity by liquid scintillation counting.

To assess distribution into red blood cells from plasma, peramivir was added to pooled fresh whole blood from each species to final concentrations of 100, 500, and 1000 ng/mL and incubated at 37ºC for 4 hours. Plasma and red blood cell samples were analyzed for radioactivity by liquid scintillation counting.

Results
Less than 18% of peramivir was protein-bound in plasma from all species evaluated (Table 1). Plasma protein binding was independent of concentration for all species. There was a trend towards higher plasma protein binding in human males compared to females, but this slight difference is not expected to be clinically relevant. Peramivir partition coefficient values were small in all species, indicating a marked preference for plasma over red blood cells (Table 2).

Table 1: Peramivir protein binding in plasma (source: Study Report Table 1)

Species	10 ng/ml	100 ng/ml	500 ng/ml	1000 ng/ml
Mouse	13.76 (8.45)	8.88 (4.56)	7.22 (2.07)	8.42 (2.15)
Rat	7.17 (1.02)	6.83 (7.53)	2.96 (5.17)	9.26 (6.00)
Rabbit	10.15 (1.88)	11.81 (4.02)	9.59 (2.33)	8.96 (2.42)
Dog	12.38 (6.84)	17.74 (3.56)	9.31 (2.23)	10.12 (2.67)
Monkey	5.08 (5.83)	7.84 (5.55)	3.88 (2.24)	5.22 (0.89)
Human Male	12.29 (1.97)	10.87 (2.24)	10.04 (2.34)	12.26 (3.11)
Human Female	9.43 (4.67)	8.19 (2.97)	7.93 (0.82)	6.54 (7.85)

Table 2: Partition coefficient (K_p) values of peramivir in whole blood (source: Study Report Table 2)

Species	^{14}C-RWJ-270201 Concentration (ng/mL) 100	500	1000
Mouse	-0.016 (0.004)	-0.019 (0.007)	0.044 (0.010)
Rat	0.013 (0.005)	-0.040 (0.006)	-0.017 (0.016)
Rabbit	-0.069 (0.006)	-0.021 (0.012)	-0.062 (0.005)
Dog	-0.071 (0.013)	-0.032 (0.011)	-0.081 (0.005)
Monkey	-0.037 (0.005)	-0.048 (0.003)	-0.032 (0.016)
Human Male	-0.055 (0.039)	-0.038 (0.008)	-0.043 (0.005)
Human Female	-0.102 (0.008)	-0.106 (0.021)	-0.082 (0.011)

Conclusion

The extent of peramivir binding to human plasma proteins was low (<18%) in plasma samples from mice, rats, rabbits, dogs, monkeys, and humans. Red blood cell partitioning of peramivir was negligible.

DM98357: In vitro metabolism of the anti-infective compound RWJ-270201

Introduction
In this study, the in vitro metabolism of peramivir in the hepatic S9 fractions of rat, dog, and human was assessed and any resultant metabolites were quantified and identified.

Materials and Methods
Peramivir (100 ug/mL) was incubated with male Sprague-Dawley rat, male beagle dog, and male and female human pooled hepatic S9 fractions with an NADPH-generating system for 30 and 60 minutes at 37ºC. Control incubations containing peramivir but no S9 fractions were also included. Samples were analyzed by mass spectrometry.

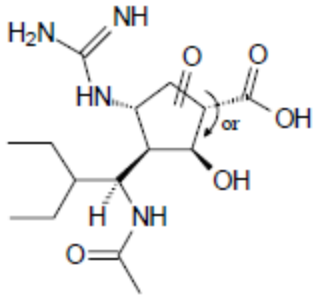
Results
Unchanged peramivir was the predominant moiety in the S9 incubates (Table 1). One metabolite (M1) from the 60 minute incubates of rat and human hepatic S9 fractions was tentatively identified as oxo-peramivir (Figure 1); no other metabolites were detected in the S9 fractions from any species.

Table 1: Relative percent of sample in S9 fractions (source: Study Report Table 1)

Species	Rat		Dog		Human	
Analyte	30 min	60 min	30 min	60 min	30 min	60 min
RWJ-270201	98	98	100	100	98	96
M1 (Oxo-RWJ-270201)	<2	2	-	-	2	4

- : not detected

Figure 1: Chemical structure of M1 (source: Study Report Figure SD1)



Conclusion
Peramivir is not extensively metabolized in rat, dog, or human hepatic S9 fractions. Only one metabolite, M1, was detected in rat and human S9 fractions but not in dog. This metabolite was formed from oxidation of the cyclopentyl ring.

7SHIOP: Study on P-glycoprotein mediated drug interaction of (b) (4)

Introduction
In this study, the bidirectional permeability of peramivir and the effect of peramivir on the bidirectional permeability of the P-gp substrate digoxin were determined using human colon carcinoma (Caco-2) cells.

Materials and Methods
Caco-2 cells were grown to confluence on 12-well Transwell® plates. To assess P-gp transport of peramivir, forward (apical to basolateral, A to B) and reverse (basolateral to apical, B to A) permeability of peramivir (3, 30, and 300 uM) or the known P-gp substrate digoxin (10 uM) was determined over 120 minutes. The efflux ratio was calculated as the average reverse apparent permeability (P_{app}) divided by the average forward P_{app} ($P_{app,B:A}/P_{app,A:B}$). Immediately following completion of the assay, Lucifer yellow permeability was measured to evaluate membrane integrity. Experimental conditions were conducted in triplicate and samples were analyzed by LC-MS/MS.

To assess peramivir inhibition of P-gp transport, forward (apical to basolateral, A to B) and reverse (basolateral to apical, B to A) permeability of digoxin (10 uM) was determined over 120 minutes in the presence of peramivir (300 uM) or the known inhibitors cyclosporine A (10 uM) or ketoconazole (10 uM). The efflux ratio was calculated as the average reverse apparent permeability (P_{app}) divided by the average forward P_{app} ($P_{app,B:A}/P_{app,A:B}$). Immediately following completion of the assay, Lucifer yellow permeability was measured to evaluate membrane integrity. Experimental conditions were conducted in triplicate and samples were analyzed by LC-MS/MS.

Results
At concentrations up to 300 uM, peramivir had low permeability in both directions, with efflux ratios ranging from 0.27-1.28, indicating no significant efflux transport (Table 1). In the presence of 300 uM peramivir, digoxin efflux was 12.3% lower, compared to 88.7 and 93.7% lower in the presence of CsA and ketoconazole, respectively (Table 2), indicating that peramivir is not a significant P-gp inhibitor.

Table 1: Bidirectional permeability of peramivir across Caco-2 monolayers (source: Study Report Table 1)

Treatment	Direction	Parameter	Repl. 1	Repl. 2	Repl. 3	Average ± STD	B-A /A-B P_{app} Ratio
Peramivir (3 µM)	A-B	$P_{app, A-B}$ ($\times 10^{-6}$ cm/s)	0.31	1.15	0.85	0.77 ± 0.43	0.27
		% Recovery	91.6	88.3	92.4	90.7 ± 2.2	
	B-A	$P_{app, B-A}$ ($\times 10^{-6}$ cm/s)	0.21	0.18	0.24	0.21 ± 0.03	
		% Recovery	96.3	91.0	95.0	94.1 ± 2.7	
Peramivir (30 µM)	A-B	$P_{app, A-B}$ ($\times 10^{-6}$ cm/s)	0.11	0.15	0.10	0.12 ± 0.03	1.28
		% Recovery	61.6	73.6	86.1	73.8 ± 12.3	
	B-A	$P_{app, B-A}$ ($\times 10^{-6}$ cm/s)	0.09	0.26	0.10	0.15 ± 0.10	
		% Recovery	101	100	99.3	100 ± 0.9	
Peramivir (300 µM)	A-B	$P_{app, A-B}$ ($\times 10^{-6}$ cm/s)	0.14	0.16	0.91	0.40 ± 0.44	0.30
		% Recovery	77.2	84.7	69.3	77.0 ± 7.7	
	B-A	$P_{app, B-A}$ ($\times 10^{-6}$ cm/s)	0.12	0.12	0.12	0.12 ± 0.00	
		% Recovery	98.7	97.4	97.4	97.8 ± 0.8	
Digoxin (10 µM)	A-B	$P_{app, A-B}$ ($\times 10^{-6}$ cm/s)	0.91	0.60	0.63	0.71 ± 0.17	19.3
		% Recovery	94.5	97.0	108	100 ± 7.5	
	B-A	$P_{app, B-A}$ ($\times 10^{-6}$ cm/s)	12.5	14.8	13.8	13.7 ± 1.14	
		% Recovery	98.1	106	105	103 ± 4.4	

NOTE: All monolayer replicates passed the post-experiment integrity test (lucifer yellow $P_{app} < 0.8 \times 10^{-6}$ cm/s).

Table 2: Bidirectional permeability of digoxin across Caco-2 monolayers in the presence of peramivir or the P-gp inhibitors ketoconazole or CsA (source: Study Report Table 2)

Treatment	% Recovery Avg. ± STD, N=3	P_{app} ($x 10^{-6}$ cm/s) R1	P_{app} ($x 10^{-6}$ cm/s) R2	P_{app} ($x 10^{-6}$ cm/s) R3	P_{app} ($x 10^{-6}$ cm/s) Avg. ± STD, N=3	B-A/A-B P_{app} Ratio	% Inhibition from Control Values
Digoxin Alone Control A-B Direction	100.0 ± 7.5	0.91	0.60	0.63	0.71 ± 0.17	19.3	Control
Digoxin Alone Control B-A Direction	103.1 ± 4.4	12.5	14.8	13.8	13.7 ± 1.14		
Digoxin + CSA A-B Direction	96.9 ± 4.5	2.19	2.36	2.19	2.25 ± 0.10	2.18	88.7
Digoxin + CSA B-A Direction	106.0 ± 5.2	3.62	4.77	6.30	4.90 ± 1.35		
Digoxin + Ketoconazole A-B Direction	121.2 ± 1.2	5.25	5.40	5.58	5.41 ± 0.17	1.22	93.7
Digoxin + Ketoconazole B-A Direction	103.9 ± 2.9	6.88	6.28	6.58	6.58 ± 0.30		
Digoxin + Peramivir A-B Direction	90.9 ± 6.6	1.18	0.97	1.06	1.07 ± 0.11	16.9	12.3
Digoxin + Peramivir B-A Direction	97.2 ± 5.3	14.3	20.2	19.6	18.0 ± 3.25		

NOTE: All cell monolayers had preserved integrity (post-experiment lucifer yellow $P_{app} < 0.8 \times 10^{-6}$ cm/s).

Conclusion

Over the concentration range of 3-300 uM, peramivir did not exhibit significant directional transport across Caco-2 monolayers, indicating that it is not a P-gp substrate. In addition, digoxin efflux across Caco-2 monolayers was not substantially altered by 300 uM peramivir, indicating that it is not a P-gp inhibitor.

DM01372: Transport characteristics of RWJ-270201 in various cell lines

Introduction
In this study, peramivir transport by P-gp was assessed in MDR1-MDCK cells and transport by P-gp and MRPs was assessed in Caco-2 cells. The inhibitory potential of peramivir on P-gp was also evaluated in MDR1-MDCK cells.

Materials and Methods
To evaluate peramivir P-gp transport, MDR1-MDCK and MDCK parent cells were grown to confluence on cell culture inserts. To assess P-gp transport of peramivir, forward (apical to basolateral, A to B) and reverse (basolateral to apical, B to A) permeability of ^{14}C-peramivir (100 uM) was determined over 180 minutes. To evaluate the potential for P-gp inhibition by peramivir, forward and reverse permeability of ^{3}H-digoxin (5 uM) was determined in the presence of peramivir (100 uM) or the known P-gp inhibitor ketoconazole (100 uM) was determined over 180 minutes. The efflux ratio was calculated as the average reverse apparent permeability (P_{app}) divided by the average forward P_{app} ($P_{app,B:A}/P_{app,A:B}$). Experimental conditions were conducted in triplicate and samples were analyzed by liquid scintillation counting.

Caco-2 cells (passage 25-30) were grown to confluence for at least 21 days on 6-well plates. To assess P-gp and MRP transport of peramivir, forward and reverse permeability of peramivir (100 uM) in the presence of the OAT and non-specific MRP inhibitor probenecid (500 uM), the OAT and MRP inhibitor indomethacin (200 uM), or the OCT inhibitor cimetidine (500 uM) was determined over up to 180 minutes. Experimental conditions were conducted in triplicate and samples were analyzed by LC-MS/MS.

Results
The net flux ratio of peramivir was 1.2 and 0.82 in MDR1-MDCK and MDCK cells, respectively, indicating lack of P-gp transport. The net flux ratio of digoxin in MDR1-MDCK cells was 17.8 and 18.5 in the absence or presence of peramivir, respectively, indicating lack of P-gp inhibition. Probenecid, a nonspecific MRP inhibitor, did not alter peramivir transporter, suggesting that peramivir is not an MRP substrate. Inhibition of A:B transport was observed in the presence of cimetidine and indomethacin (net flux ratios of 1.17 and 0.97, respectively)), suggesting that peramivir could be a substrate for an unidentified transporter.

Conclusion
Based on the results of this study, peramivir is neither a substrate nor inhibitor of P-gp. Peramivir may be a weak substrate of an unidentified transporter; however, transport interactions are not likely to be clinically significant based on the magnitude of the interaction observed here.

DM98399: In vitro assessment of the potential for RWJ-270201 to inhibit the cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 in human liver microsomes

Introduction
In this study, the potential for peramivir to inhibit human cytochrome P450 (CYP) isoforms was assessed using isoform-specific probe substrates in human hepatic microsomal fractions.

Materials and Methods
Probe substrates were incubated with human liver microsomes and NADPH at 37ºC in the presence of peramivir (up to 100 uM) or control inhibitors (Table 1). Drug concentrations were assessed by HPLC and were used to calculate IC_{50} values.

Table 1. CYP isoform-specific probe substrates and control inhibitors

CYP isoform	Probe substrate	Conc. (uM)	Inc. time (min)	Control inhibitor	Conc. range (uM)
CYP1A2	phenacetin	100	30	α-napthoflavone	25
CYP2A6	coumarin	1	20	tranylcypromine	250
CYP2C9	tolbutamide	150	40	sulfaphenazole	50
CYP2C19	S-mephenytoin	50	30	tranylcypromine	20
CYP2D6	dextromethorphan	16	15	quinidine	1
CYP2E1	chlorzoxazone	50	20	diethyl-dithiocarbamate	10
CYP3A4	testosterone	50	10	ketoconazole	5

Results
Peramivir IC_{50} values were high for all CYP isoforms evaluated (>100 uM). In contrast, control inhibitors (except for tranylcypromine) had low IC_{50} values, indicating potent inhibition.

Conclusion
Peramivir did not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at concentrations up to 100 uM.

DM99339: An investigation of the potential for RWJ-270201 to induce CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in cultured primary human hepatocytes

Introduction
In this study, the potential of peramivir to potentiate induction of drug metabolizing enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP3D6, CYP2E1, and CYP3A4) was evaluated using primary cultured human hepatocytes from one female donor.

Materials and Methods
Cultured human hepatocytes were plated in collagen coated 24-well plates and incubated in 50, 200, 1000, or 10,000 ng/mL peramivir, vehicle control, or positive control inducers (CYP1A: omeprazole, CYP2D6 and CYP3A4: rifampicin) for three days. Induction of activity was measured using catalytic activity assays (probe substrates included CYP1A2: 2 uM ethoxyresorufin, CYP2A6: 100 uM coumarin, CYP2C9: 50 uM tolbutamide, CYP2C19: 100 uM S-mephenytoin, CYP2D6: 160 uM dextromethorphan, CYP2E1: 300 uM chlorzoxazone, CYP3A4: 125 uM testosterone) and HPLC analysis. Well conditions were assessed in triplicate.

Results and Conclusion
At concentrations up to 10 uM, peramivir did not induce activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP3D6, CYP2E1, or CYP3A4 to a statistically significant degree, nor was there an obvious relationship between peramivir concentration and induction of activity.

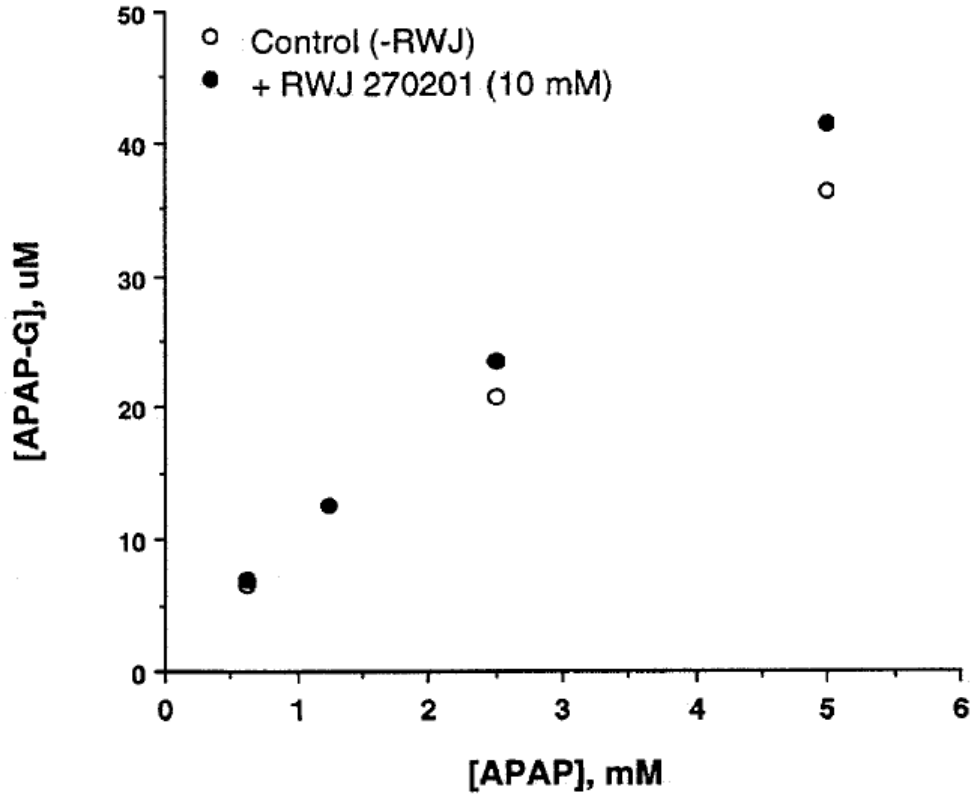
DM99401: RWJ-270201 in vitro interaction with acetaminophen

Introduction
In this study, the potential of peramivir to inhibit the glucuronidation of acetaminophen (APAP) to form acetaminophen glucuronide (APAP-G) was evaluated.

Materials and Methods
APAP (0.625-5 mM) was incubated with male human liver microsomes and NADPH at 37ºC for 1 h in the presence or absence of peramivir (0-10 uM). Drug concentrations were assessed by HPLC and were used to calculate IC_{50} values.

Results and Conclusion
At concentrations up to 10 uM, peramivir did not substantially influence glucuronidation of APAP (Figure 1); thus, peramivir and acetaminophen may be taken concurrently with a pharmacokinetic interaction.

Figure 1: APAP glucuronidation in the presence (closed circles) or absence (open circles) of peramivir 10 uM (source: Study Report Figure 5)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFRY FLORIAN

08/22/2014

Signing for Islam Younis and Leslie Chinn (8/22/2014). DARRTS entry issue prohibited their signing of the review.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206426**	**Brand Name**	**RAPIVAB**
OCP Division (I, II, III, IV, V)	**IV**	**Generic Name**	**Peramivir**
Medical Division	**DAVP**	**Drug Class**	**Neuraminidase Inhibitor**
OCP Reviewer	**Vikram Arya, Ph.D.**	**Indication(s)**	**Treatment of Acute Uncomplicated Influenza in Patients 18 years and older**
OCP Team Leader	**Islam Younis, Ph.D.**	**Dosage Form**	**200 mg (20 mL vial)**
Pharmacometrics Reviewer	**Leslie Chinn, Ph.D.**	**Dosing Regimen**	**Single 600 mg dose, administered by i.v. infusion for a minimum of 15 minutes**
Date of Submission	**December 23, 2013**	**Route of Administration**	**Intravenous**
Estimated Due Date of OCP Review	**July 23, 2014**	**Sponsor**	**Biocryst**
Medical Division Due Date	**August 23, 2014**	**Priority Classification**	**Standard**
PDUFA Due Date	**December 23, 2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**10**	**5**	Only bioanalytical methods pertaining to quantification of peramivir in plasma and urine will be reviewed
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	**X**	**6**	**6**	Includes one study that assess the p-gp transporter assessment
Blood/plasma ratio:				
Plasma protein binding:	**X**	**2**	**2**	
Pharmacokinetics (e.g., Phase I) -	**X**	**4**	**0**	Trials BCX1812-112,-116, 117, and 118 will not be reviewed as these studies only evaluated either the intramuscular formulation or the subcutaneous formulation (-118). The applicant proposes to market the intravenous formulation.
Healthy Volunteers-				
single dose:	**X**	1	**1**	
multiple dose:	**X**	4	**4**	

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Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	**X**			Studies counted under multiple dose studies
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2	2	
In-vivo effects of primary drug:	X	1	1	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1	1	
renal impairment:	X	1	1	
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1	1	
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability	X	2	2	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	N/A			Intravenous formulation
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		35	26	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____YES____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

VIKRAM ARYA	01/29/2014
Reviewing Clinical Pharmacologist	Date
ISLAM YOUNIS	01/29/2014
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIKRAM ARYA
01/29/2014

ISLAM R YOUNIS
01/30/2014