CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206426Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	206426
Priority or Standard	Standard
Submit Date(s)	December 23, 2013
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Division / Office	Division of Antiviral Products/ Office of Antimicrobial Products
Reviewer Name(s)	Peter Miele, MD
Review Completion Date	August 22, 2014
Established Name	Peramivir
(Proposed) Trade Name	RAPIVAB
Therapeutic Class	Influenza neuraminidase inhibitor (NAI)
Applicant	BioCryst Pharmaceuticals, Inc.
Formulation(s)	200 mg (20 mL) vial
Dosing Regimen	600 mg IV single dose
Indication(s)	Treatment of acute uncomplicated influenza
Intended Population(s)	Adults 18 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of peramivir (RAPIVAB) 600 mg as a single-dose intravenous (IV) infusion for the treatment of adults with acute uncomplicated influenza who are symptomatic for less than two days. This recommendation is based on review of the clinical pharmacology, safety, and effectiveness data submitted in New Drug Application (NDA) 206426.

In this application, clinical effectiveness data from an adequate and well-controlled Phase 2 trial (Study 0722T0621) in adults with acute uncomplicated influenza demonstrated that a single dose of IV peramivir 600 mg resulted in a 22 hour reduction in median time to resolution of influenza symptoms compared with placebo, a difference that was statistically significant and persuasive to support an efficacy claim. An integrated analysis with additional data from three placebo-controlled Phase 2 and 3 trials of intramuscular (IM) peramivir, in comparable adult populations with acute influenza, further corroborated the treatment benefit described in Study 0722T0621. All four of these trials evaluated anti-influenza effectiveness in a manner that was consistent with FDA guidance and which had been used previously in registrational trials of oseltamivir and zanamivir, two approved anti-influenza products in the same pharmacologic class as peramivir. Further support to the efficacy claim was provided by the observation of a consistent peramivir treatment effect across multiple secondary endpoints and among various subgroups defined by age, race, sex, region, and influenza A subtype in pooled analyses.

The application included data not only from the clinical trials in adults with acute uncomplicated influenza but also from clinical trials in hospitalized patients and pediatrics, as well as safety information from the 2009 Emergency Use Authorization, during which IV peramivir was administered to approximately 1,274 hospitalized patients in the United States. In addition, the application included summaries of the IV peramivir postmarketing experience in Japan, where the product was approved in 2010 and has been used in an estimated nearly 800,000 patients. According to my review of the clinical trial data submitted in support of the proposed indication, and considering the extensive safety information available from various other sources, the safety profile of IV peramivir is acceptable and no deficiencies were identified in this application that would preclude approval.

Although the pivotal Study 0722T0621 demonstrated similar efficacy between the 300 mg and 600 mg doses of IV peramivir, several secondary analyses found a dose-ordered response. This and modeling results from a pharmacokinetic-pharmacodynamic

model developed by the Applicant suggest that the 600 mg dose will likely benefit more patients than would a lower dose of peramivir. In the absence of any observed dose dependency for adverse events, the 600 mg dose of IV peramivir is recommended for approval.

It should be noted that the clinical data submitted in this application were inconclusive regarding the efficacy of peramivir against influenza B, as the numbers of subjects enrolled in the clinical trials with this influenza type were small (12% overall). Nonclinical data, however, have demonstrated potent activity of peramivir against influenza B in vitro and in vivo, comparable to that observed with oseltamivir and zanamivir. Since peramivir shares the same mechanism of action as these two other drugs, both of which have demonstrated effectiveness against influenza B in clinical practice, there is little reason to suspect that peramivir will not have adequate clinical activity against influenza B as well. As such, this limitation of the data should not impede approval of IV peramivir or restrict its indication, but labeling should point out these deficiencies.

Finally, the recommendation for approval is dependent on satisfactory resolution of the deficiencies observed during inspection of the sole manufacturing site of peramivir drug product (b) (4) At the time of this writing, those issues were still under review by the Office of Compliance. Please see the Division Director memorandum for final outcome of those deliberations.

1.2 Risk Benefit Assessment

Given its favorable safety profile and low potential for drug interactions, the risk associated with IV peramivir therapy for the treatment of acute uncomplicated influenza is low. No significant safety signals were identified in the clinical development program or in postmarketing that would warrant special vigilance and no contraindications are proposed for labeling. Intravenous administration of any medication may be associated with a very low incidence of infusion site reactions, such as extravasation, phlebitis, or angiopathy, or vasovagal reactions associated with IV insertion. Review of the clinical data submitted in support of this application, however, did not reveal an increased risk of these types of events with IV peramivir. It is recommended that IV peramivir be infused over at least 15 minutes and administered by a qualified healthcare professional. As such, any potential infusion-related events can be readily monitored clinically. Also, while there were no definite signals of hypersensitivity or anaphylaxis-type reactions in the submitted data, a low incidence of rash events was noted in the clinical development program. While none of these events was serious, rare cases of serious skin reactions have been reported in other clinical trial settings and in postmarketing. Therefore, prescribers should remain alert for the occurrence rash events and counsel patients accordingly. Similarly, while there was no compelling evidence in the clinical trial data to suggest an association between peramivir treatment and neuropsychiatric events in adults, cases of abnormal behavior have been reported in postmarketing in Japan, particularly among children. Patients treated with IV

peramivir therefore should be counseled about the risk of neuropsychiatric events with influenza and monitored for signs of abnormal behavior.

The clinical benefit of IV peramivir in the treatment of adults with acute uncomplicated influenza is evidenced by the clinical trial data described in Section 1.1. It is also worth noting that peramivir would be the third approved drug in the neuraminidase inhibitor class. Since first approval of oseltamivir and zanamivir 15 years ago, there has been considerable clinical experience with neuraminidase inhibitors, which has not altered their favorable risk-benefit profile. It is not unreasonable to expect that the post-approval experience with peramivir will be much different. The advantage peramivir has over these other two drugs is in its IV route of administration and single dosing regimen. As early intervention is essential to the adequate treatment of influenza, a long-acting product that can be administered at the time of presentation and that has rapid pharmacokinetic absorption would be a valuable addition to the anti-influenza drug armamentarium. Moreover, the dosage and administration characteristics of peramivir eliminate patient-related factors that might complicate therapy, such as delayed initiation of treatment, noncompliance with prescription, medication error, or nonadherence to a full 5-day treatment course. Also, because absorption of IV peramivir bypasses the gastrointestinal system, the product would be of benefit in patients unable to tolerate oral intake due to gastrointestinal distress, which is not uncommon with acute influenza illness. For these reasons, it is envisioned that IV peramivir would be of benefit in emergency room settings or urgent care facilities with infusion capabilities. Although it has not been shown to decrease transmission, IV peramivir can also be beneficial in situations where assurance of rapid treatment is important, such as in treatment of close contacts of persons with high-risk factors for serious influenza disease or nursing home residents.

Another issue to consider is the potential off-label use of IV peramivir in hospitalized patients. Although the clinical trials in hospitalized influenza patients did not demonstrate a significant clinical benefit of IV peramivir in this population, it is anticipated that the product will be used in hospital settings nonetheless. The safety data from the hospitalized trials were frequently confounded; however, no new safety signals emerged with repeated daily dosing up to 10 days and the overall safety profile of IV peramivir in this population appeared similar to that observed in the trials of acute uncomplicated influenza. Labeling for IV peramivir will reflect these findings, but clinicians will need to make their own risk-benefit assessments regarding use of IV peramivir in a hospitalized patient based on these findings.

Lastly, there is a theoretical risk that a patient infected with influenza B will not derive significant clinical benefit from treatment with IV peramivir. The efficacy of peramivir against influenza B was not demonstrated in the clinical trials of acute uncomplicated influenza, but this was most likely because of low enrollment of this subgroup. The nonclinical data suggest that peramivir has activity against influenza B comparable to that seen with the other two neuraminidase inhibitors. Given that oseltamivir and

zanamivir have demonstrated effectiveness against influenza B in the postmarketing setting, and given that they share the same mechanism of action with peramivir, it is expected that IV peramivir will perform similarly against influenza B in a real world setting. Nonetheless, labeling for peramivir will inform prescribers of these limitations of the data.

In conclusion, the totality of the evidence submitted in this application suggests that the benefits of IV peramivir outweigh the potential risks. The few potential risks that may be associated with IV peramivir treatment will be clearly labeled and can be readily monitored clinically.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Risk Evaluation and Mitigation Strategies (REMS) are not warranted due to the acceptable safety profile of IV peramivir and its intended use. Routine pharmacovigilance practices are considered sufficient to maximize safe use of the product, and should provide more clarity on the possible role of peramivir in neuropsychiatric events and severe skin reactions.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarketing clinical studies under consideration at this time include the following:

- A deferred pediatric trial required under the Pediatric Research Equity Act (PREA) 21 CFR 314.55 (b) and 601.27 (b). Please refer to Section 7.6.3 for discussion of the Applicant's proposed pediatric development plan. The Applicant has not requested a Written Request at this time.

- Additional clinical evaluation of peramivir efficacy against influenza B infection. This information may be collected as part of the pediatric trial or in a separate clinical trial.

The Virology review team also recommends postmarketing requirements to submit the remainder of the clinical resistance data that were not included in the application and to determine the cross-resistance of peramivir to oseltamivir and zanamivir for all of the hemagglutinin (HA) peramivir resistance-associated substitutions not yet evaluated. In addition, an evaluation of the impact of HA substitutions noted with peramivir treatment on the influenza vaccine is recommended.

Please note that internal discussions regarding postmarketing studies were still ongoing at the time of this writing and negotiations with the Application had not yet begun. Please refer to the Division Director memorandum for final decisions regarding postmarketing studies.

2 Introduction and Regulatory Background

2.1 Product Information

Peramivir is a selective inhibitor of influenza viral neuraminidase (NA) characterized by tight binding and a slow rate of dissociation from the NA enzyme. Influenza NA is responsible for the release of new viral particles from infected cells and may also assist in the spreading of virus through the mucus within the respiratory tract. Peramivir has demonstrated activity against influenza A and B subtypes, including the 2009 novel pandemic influenza A strain (H1N1pdm09), highly pathogenic avian influenza H5N1, and the recently described novel avian influenza A (H7N9) virus.[1] Two other neuraminidase inhibitors, oseltamivir and zanamivir, are currently marketed for treatment of acute uncomplicated influenza in adults. Peramivir, a new molecular entity, would be the third neuraminidase inhibitor added to this pharmacologic class.

Established name:	Peramivir
Trade name:	RAPIVAB®
Chemical class:	New molecular entity
Pharmacologic class:	Influenza neuraminidase inhibitor (NAI)
Proposed indication:	Treatment of acute uncomplicated influenza in patients 18 years and older
Formulation:	200 mg (20 mL) vial for injection
Dose regimen:	Single 600 mg dose, administered by intravenous administration

2.2 Tables of Currently Available Treatments for Proposed Indications

Four licensed prescription influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir phosphate, an oral prodrug of the active agent oseltamivir carboxylate (Table 1).

[1] Chen Y, Weifeng L, Shigui Y. et al. Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterization of viral genome. Lancet 2013; 381: 1916-25.

Zanamivir and oseltamivir are related antiviral medications in the class of medications known as neuraminidase inhibitors (NAIs). When administered within 48 hours of illness onset, the two approved NAIs can reduce the severity and shorten the duration of acute uncomplicated influenza illness in previously healthy adults. Zanamivir and oseltamivir are active against both influenza A and B viruses, but differ in pharmacokinetics, safety profiles, route of administration, approved age groups, and recommended dosages. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension.

The adamantanes are the other class of approved influenza antiviral agents and include amantadine and rimantadine. Adamantanes are thought to interact with the viral M2 ion channel protein. When administered within 48 hours of illness onset, amantadine and rimantadine can reduce the severity and shorten the duration of acute uncomplicated influenza A illness among healthy adults; however, they have no activity against influenza B virus. In recent years, widespread adamantane resistance among influenza A virus strains (H3N2, H1N1pdm09) has made this class of medications less clinically useful. Therefore, amantadine and rimantadine are not recommended by the U.S. Centers for Disease Control and Prevention (CDC) for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.[2]

Table 1: Currently Approved Influenza Antiviral Agents

Drug Class	Generic Name	Trade Name
Neuraminidase inhibitor (NAI)	Oseltamivir phosphate	Tamiflu®
	Zanamivir	Relenza®
Adamantane	Amantadine hydrochloride	Symmetrel®
	Rimantadine hydrochloride	Flumadine®

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is not marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The adverse effects of NAIs are typically mild. Most observed adverse reactions are related to route of administration, such as nausea and vomiting with oseltamivir and bronchospasm with zanamivir. More serious events, however, have been described in postmarketing, including severe allergic reactions and dermatologic events, such as anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. In addition, there have been

[2] CDC. Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza - Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011; 60 (No. RR#1): 1-28.

postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving NAIs, including oseltamivir and zanamivir. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on drug usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. Several reviews have since found no causal link between oseltamivir and increased risk of neuropsychiatric events. [3,4] Similar events have been reported among patients not receiving antiviral treatment, as influenza itself can be associated with a variety of neurologic and behavioral symptoms which may occur in the setting of encephalitis or encephalopathy but can also occur without obvious severe disease. Nevertheless, U.S. labeling for oseltamivir and zanamivir advises that patients with influenza be closely monitored for signs of abnormal behavior.

Although it is difficult to determine a role of NAIs in both severe skin reactions and neuropsychiatric events, the draft prescribing information for peramivir proposes language describing these events similar to that found in current labeling for other NAI drugs.

The following adverse reactions have also been identified in postmarketing use of NAIs:

- Digestive: hepatitis, liver function tests abnormal
- Cardiac: arrhythmia, syncope
- Gastrointestinal disorders: gastrointestinal bleeding, hemorrhagic colitis
- Neurologic: seizure, vasovagal-like episodes
- Metabolic: aggravation of diabetes

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Peramivir (BCX1812) was first discovered at BioCryst in 1998. That same year, it was licensed to R W Johnson Pharmaceutical Research Institute (RWJPRI) for development of an oral formulation. Investigational New Drug (IND) (b) (4) for peramivir tablets was filed on April 16, 1999. In 2001, the development of peramivir tablets was stopped by RWJPRI when it was determined that the (b) (4) Full rights were returned to BioCryst and IND (b) (4)

IND 69038 for peramivir intravenous (IV) injection was filed on November 23, 2005, and Fast Track designation was granted on January 5, 2006. IND (b) (4) for peramivir intramuscular (IM) injection was filed on November 3, 2006.

[3] Blumenthals W, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. MedGenMed 2007; 9: 23.
[4] Toovey S, Rayner C, Prinssen E, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. Drug Saf 2008; 31:1097-114.

In January 2007, BioCryst was awarded an advanced development contract for the development of peramivir using both IV and IM administration by the Health and Human Services Biomedical Advanced Research and Development Authority (HHS/BARDA). Also in 2007, the rights to peramivir were licensed for certain overseas territories to Shionogi & Co., Ltd (Japan) for the development and commercialization of IV peramivir. Peramivir for IV injection was approved in Japan in 2010 (see Section 2.6).

Throughout its development, peramivir has been evaluated for two potential indications: as single-dose treatment (IV or IM) for acute uncomplicated influenza and as multiple-dose, multiple-day treatment (IV) for seriously ill patients hospitalized with influenza.

During development of the IM formulation, the dose administered increased from 150 mg to 600 mg and the formulation achieved a concentration of 150 mg/mL. For a dose of 600 mg, this resulted in a total injection volume of 4 mL, split equally between two injection sites. As such, the IM formulation was associated with an increased frequency of injection site pain and discomfort and was less well tolerated in clinical trials than the IV formulation. These injections site adverse events were more common in healthy volunteers in Phase 1 trials than in subjects with acute uncomplicated influenza enrolled in the Phase 2 and 3 trials. However, given the success of the Shionogi placebo-controlled Phase 2 trial of IV peramivir in acute uncomplicated influenza (Study 0722T0621), the injection site pain and discomfort associated with the IM route of administration, HHS/BARDA's decision to focus (b) (4) the advancement of the hospitalized influenza program to Phase 3 with IV peramivir, the development program for IM peramivir was discontinued and IND (b) (4) was inactivated on January 8, 2010.

Between 2007 and 2009, several meetings were held between BioCryst and the FDA Division of Antiviral Products (DAVP), during which the content of the clinical development program for peramivir and associated regulatory strategies were discussed. These discussions culminated in a Type A Meeting held on July 08, 2009, with agreement that the BioCryst Study BCX1812-301, a Phase 3 trial of IV peramivir in subjects hospitalized with influenza, and the Shionogi Study 0722T0621, a Phase 2 trial of IV peramivir in adults with acute uncomplicated influenza, could serve as adequate and well-controlled trials to support an application for both proposed indications.

When Study BCX1812-301 failed to meet its primary efficacy endpoint and was terminated after an interim analysis result crossed a futility boundary, further discussions were held between BioCryst and DAVP to explore alternative NDA strategies. These discussions (a Type C Meeting on April 02, 2013; a Virology Teleconference on June 25, 2013; and a Pre-NDA Meeting on June 28, 2013) resulted in the agreement that a single adequate and well-controlled trial of IV peramivir (Shionogi Study 0722T0621), supported by the BioCryst trials of IM peramivir (Studies BCX1812-211, -212 and -311), would be adequate to file a reviewable NDA with the

treatment of acute uncomplicated influenza as the sole indication. The amount and type of information from Study BCX1812-301, the terminated hospital study, to be included in peramivir labeling was also discussed. FDA noted that a limited description regarding the outcome of this trial would be considered (i.e. that the trial data did not demonstrate efficacy in this population); (b) (4)

The bioequivalence of the peramivir IM and IV formulations was established in two healthy volunteer trials across a dose range of 75 to 600 mg, inclusive. At a Type A Meeting held on December 10, 2010, DAVP noted the acceptability of efficacy and safety data generated with the IM formulation to support an NDA of IV peramivir. All clinical trials with IV or IM peramivir administration, whether sponsored by BioCryst or Shionogi, are therefore included in this application.

2.6 Other Relevant Background Information

Peramivir Marketing Approvals in Asia

1) Japan and Taiwan – RAPIACTA® (Shionogi & Co, Ltd.)

BioCryst and Shionogi entered into an exclusive license agreement in March 2007 for the development and commercialization of IV peramivir in Japan and Taiwan. In January 2010, Shionogi received regulatory approval for IV peramivir in Japan for the treatment of adults with uncomplicated seasonal influenza and launched it under the commercial name RAPIACTA® (300 mg bag and 150 mg vial for IV drip infusion). This approval was based on data from three clinical trials sponsored by Shionogi, each conducted in subjects with acute uncomplicated influenza: 1) the placebo-controlled Phase 2 Study 0722T0621 conducted in Japan; 2) the oseltamivir-controlled Phase 3 Study 0815T0631 conducted in Japan, Taiwan, and Korea; and 3) the Phase 3 Study 0815T0632 conducted in Japan in subjects at high risk for complications of influenza. According to the prescribing information for RAPIACTA, the recommended adult dosage is 300 mg administered as a single IV infusion. For patients at risk of increased severity due to complications or other factors, a dose of 600 mg may be administered by single IV infusion, which may be repeated daily depending on clinical symptoms.[5] In October 2010, based on clinical trial data from the Shionogi Phase 3 pediatric Study 0918T0633, an expanded use indication for RAPIACTA was approved for the treatment of children and infants with influenza. RAPIACTA has not yet been approved in Taiwan.

There have been no regulatory actions limiting the use of RAPIACTA. However, there have been two safety related updates to Japanese labeling approval:

[5] Shionogi & Co., Ltd. Rapiacta (peramivir hydrate) for intravenous drip infusion prescribing information; revised 2013.

- In March 2011, following an internal analysis by Shionogi, 'vascular pain' was added as a nonserious adverse drug reaction in the "Other Adverse Reactions" section of the label, and 'shock' was added to the "Clinically Significant Adverse Drug Reactions" section.

- In July 2013, hepatic dysfunction and jaundice were added to both the "Precautions" and "Clinically Significant Adverse Drug Reactions" sections of the label at the request of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). This was based on a few reports of serious adverse hepatic events that occurred postmarketing and for which a role of peramivir could not be excluded by the PMDA.

Please refer to Section 7.3.5 for analyses of the submission specific safety concerns, including infusion site reactions, orthostatic hypotension/shock, and hepatic effects observed in this application, and to Section 8 for further discussion of the global postmarketing safety experience with IV peramivir.

2) South Korea – PERAMIFLU® (Green Cross Corp.)

In June 2006, BioCryst and Green Cross Corp. entered into an agreement to develop and commercialize peramivir in South Korea. In August 2010, Green Cross Corp. received authorization to market and manufacture IV peramivir in South Korea to treat patients with influenza A & B viruses, including 2009 pandemic H1N1 and avian influenza. Green Cross Corp. launched peramivir in Korea under the commercial name PERAMIFLU®. According to the prescribing information, the recommended adult dosage is 300 mg IV administered as a single infusion.[6]

3) China

On April 6, 2013, the China State Food and Drug Administration announced expedited approval of IV peramivir to treat a new strain of H7N9 avian influenza; however, the data upon which this approval was based are not clear.[7] BioCryst does not have any patents, partnerships, or in-country operations in China; Guangzhou Nanxin Pharmaceutical has reportedly been granted approval to produce peramivir in China.[8]

Emergency Use Authorization of 2009 for IV Peramivir

On October 23, 2009, FDA issued an Emergency Use Authorization (EUA) for IV peramivir to treat suspected or confirmed 2009 H1N1 influenza A virus infection. This was the first EUA issued for an unapproved drug. Eligible hospitalized patients were

[6] Green Cross Corp. Peramiflu (peramivir hydrate) injection prescribing information; 2010.
[7] Dawson K. "China OKs US-made bird flu drug." China Daily, April 10, 2013.
[8] Anonymous. "Guangzhou Nanxin to mass produce bird flu drug peramivir." Want China Times, April 13, 2013.

unresponsive to or unable to tolerate available antivirals or lacked dependable oral or inhaled drug delivery routes. Peramivir IV was distributed to requesting physicians by the CDC. From October 23, 2009 to June 23, 2010, when the EUA was terminated, the CDC received 1,371 clinician requests for peramivir and delivered 2,129 five-day adult treatment course equivalents of peramivir to 563 hospitals. Based on data requests made to treating physicians, approximately 1,274 hospitalized patients received peramivir through the EUA program. The evaluation of safety of IV peramivir in hospitalized patients during the EUA is discussed in further detail in Section 7.7.

Current Peramivir Clinical Development Plans

Other than one trial to fulfill a post-marketing commitment in Japan, no clinical trials of peramivir are currently ongoing, and except for a proposed U.S. pediatric trial (see Section 7.6.3 “Pediatric Study Plan”), no further clinical trials are planned.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was generally well organized and easy to navigate. The datasets were sufficiently complete and adequately formatted to permit a complete and timely review. There were instances in the laboratory datasets where multiple and differing laboratory test results (e.g. neutrophil counts) were reported for a particular subject, date and time. The Applicant took remedial action by re-submitting the datasets to include the correct test codes and thus was able to resolve these issues across all datasets.

3.2 Compliance with Good Clinical Practices

The pivotal Study 0722T0621was conducted in Japan in accordance with Good Clinical Practice (GCP). As part of the Pre-EUA activities of 2009, FDA inspected three clinical sites that participated in Study 0722T0621, as well as Shionogi headquarters and the Contract Research Organization (CRO) that conducted the trial. No major observations resulted from these inspections.

In support of this application, five clinical investigator sites that participated in the BioCryst-sponsored Studies BCX1812-211 and BCX1912-212 were inspected by the Office of Scientific Investigations, Division of Good Clinical Practice Compliance. The five sites were selected based primarily on enrollment rates, percentage of subjects meeting the primary endpoint, adverse event reporting or numbers of protocol violations. Based on the inspection findings, the data generated at four of the five clinical sites were found to be reliable and acceptable in support of this application.

One clinical site (investigator John Michael Wise; Site 60 in Study BCX1812-211), however, was found to have significant regulatory violations. All subject records for Study BCX1812-211 at this site were inadvertently shredded. Since this investigator participated in all three BioCryst trials of IM peramivir (Site 700 in Study BXC1812-311 and Site 419 in Study BCX1812-212), subject records were inspected for these other two trials as well. Subject records for Study BCX1812-311 were also found to have been discarded; however, subject records for Study BXC1812-212 were available and appeared to be complete. As a result of the inspection findings, a Form 483 and a Warning Letter were issued to the site investigator and data generated at this site for Studies BXC1812-211 and -311were not used in support of the application. Specifically, subject data from Site 60 (n=14) and Site 700 (n=3) in Studies BXC1812-211 and -311, respectively, were excluded from the analyses of peramivir efficacy and safety.

Please refer to the Clinical Inspection Summary by Dr. Antoine El-Hage for full details of the inspections.

3.3 Financial Disclosures

Refer to the Clinical Investigator Financial Disclosure Review in Section 9.4.

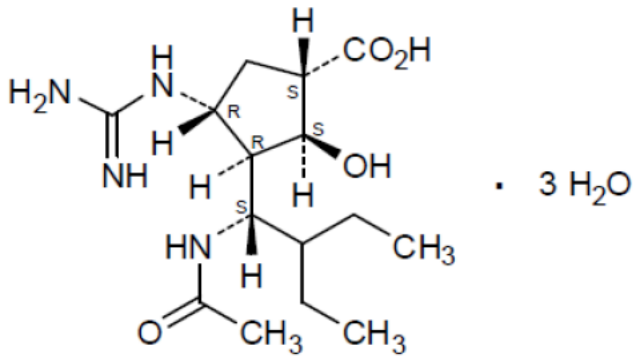
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the Chemistry Manufacturing and Controls Review by Dr. Fuqiang Liu for full details.

The chemical name for peramivir is (1S,2S,3R,4R)-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamino)-2-hydroxycyclopentanecarboxylic acid, trihydrate. The peramivir molecular formula is $C_{15}H_{28}N_4O_4 \cdot 3H_2O$ and the molecular weight is 382.45 daltons. The chemical structure is provided in Figure 1.

Figure 1: Peramivir Structure



The peramivir drug product is a clear, colorless, sterile, isotonic solution for intravenous administration. The product contains 10 mg/mL of peramivir in 0.9% sodium chloride solution. This formulation has not changed throughout the clinical development program, with the exception of the addition of a pH adjustment to pH 5.5 - 8.5 by either (b) (4) sodium hydroxide or (b) (4) hydrochloric acid (b) (4). A neutral pH demonstrated the best stability and potential for a long shelf life; therefore, a pH of 5.5 - 8.5 range was targeted for the product. Peramivir injection is stable at room temperature and is compatible with Sodium Chloride Injection, USP (0.9%, 0.45%), Dextrose USP (5%) and Lactated Ringer's Injection, USP. The proposed adult dose of 600 mg is prepared by transferring 60 mL of peramivir solution to an empty sterile IV infusion bag and adding 40 mL of a compatible USP IV infusion solution. Peramivir is administered as a single IV infusion delivered over a minimum of 15 minutes.

This application includes two manufacturers of drug substance, (b) (4) and one manufacturer of drug product, (b) (4) The manufacturing process was developed and validated at (b) (4) and subsequently transferred to (b) (4) using a technology transfer. The chemical process used at both facilities is the same with minor differences in the process parameters, which per the Applicant do not impact the quality of peramivir manufactured at the two facilities.

As part of pre-EUA activities during 2009, all three facilities were inspected by FDA:

- (b) (4) Observations were noted and a Form 483 was issued. Complete resolution was reached with FDA. Of note, all batches produced at (b) (4) were prior to the inspection. Per the Applicant, as of 2015, (b) (4) will no longer support any manufacturing activities for drug substance. However, a significant quantity of drug substance that was manufactured after the process validation at (b) (4) remains in inventory. The Applicant intends to use this drug substance commercially. Once exhausted, the Applicant will withdraw (b) (4) as a manufacturer from the NDA.
- (b) (4) No observations were noted.

- [redacted] (b) (4) Observations were noted, a Form 483 was issued, and a complete resolution was reached with FDA.

During a facility inspection for another product in 2013, however, numerous observations were noted at [redacted] (b) (4) resulting in a Warning Letter. A follow-up inspection in 2014 resulted in a Form 483 being issued again. Consequently, all manufacturing activities at the facility have been suspended pending resolution of the deficiencies, which were widespread and systemic in nature. As of this writing, the deficiencies were still being addressed and it was not clear whether they would be resolved in time to approve this application. Please refer to the review from the Office of New Drug Quality Assessment (ONDQA) for final decision.

4.2 Clinical Microbiology

Please refer to the Virology Review by Dr. Takashi Komatsu for full details.

The influenza neuraminidase NA enzyme is a surface glycoprotein that cleaves sialic acid residues from glycoproteins and glycolipids on the host cell. NA is responsible for the release of newly synthesized virus particles from infected cells, facilitating the spread of virus through the mucus within the respiratory tract.[9] The amino acid residues that define the enzyme's active site are highly conserved among influenza strains, making NA an attractive target for antiviral activity.

Peramivir is a potent and selective inhibitor of NA enzymes and has demonstrated potent activity against a number of influenza strains in vitro and in vivo.

In Vitro

When tested in vitro against laboratory strains and clinical isolates of seasonal influenza A, the 2009 pandemic H1N1 influenza A, and influenza B viruses, peramivir was equivalent to or more potent than oseltamivir carboxylate (OSE-C), the active metabolite of oseltamivir, and zanamivir. Similar results were observed whether antiviral activity was measured by inhibition of NA activity or inhibition of viral growth in cell culture assays using various endpoints (inhibition of viral cytopathic effects as measured by plaque numbers or neutral red uptake, virus titers from infected cells, and/or expression of viral nucleoprotein).

In biochemical studies using the neuraminidase inhibition assay as the endpoint, the median 50% inhibitory concentration (IC_{50}) value of peramivir ranged from 0.16 nM against influenza A/H1N1; 0.03-0.5 nM against influenza A/H1N1pdm09; 0.17 nM against influenza [redacted] (b) (4); 0.13 nM against influenza A/H3N20; 0.40 nM against

[9] Calfee D, Hayden F. New approached to influenza chemotherapy. Neuraminidase inhibitors. Drugs 1998; 56 (4): 537-53.

influenza A/H5N1; and 0.99 nM against influenza B virus. The half maximal effective concentration (EC_{50}) value of peramivir using a plaque reduction assay as the endpoint ranged from 3.45 nM , <1 nM, 0.38 nM, 0.3 nM, and 39 nM against influenza A/H1N1, (b) (4), A/H3N2, (b) (4), and influenza B virus, respectively. Of note, the activity of peramivir, as with oseltamivir and zanamivir, is less against influenza B virus compared to influenza A. In vitro binding affinity studies showed that peramivir has a higher binding affinity for NA (N1 and N9) than do the other NAIs. As was the case with the biochemical studies, the activity of peramivir was less against influenza B virus than influenza A. The relationship between antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, or inhibition of in vivo influenza virus replication and clinical benefit in humans has not been established.

Peramivir showed selectivity in vitro for viral NA when compared with bacterial enzymes and human sialidase enzymes. Peramivir is not active against adenovirus, rhinovirus, respiratory syncytial virus, parainfluenza virus type 3, or measles virus.

In Vivo

Peramivir was evaluated for antiviral activity in mouse (IV, IM, oral, and intranasal routes of administration), ferret (IV, IM, and oral administration), and cynomolgus monkey (IV and oral administration) models of influenza. The results of these studies were consistent with peramivir having antiviral activity in prophylactic and treatment scenarios.

The efficacy of a single IV injection of peramivir was comparable to that of 5 days of oral treatment with peramivir or oseltamivir in the mouse model of influenza. Representative studies used influenza A/PR/8/34 (H1N1), A/Kumamoto/Y5/67 (H2N2), A/Victoria/3/75 (H3N2), B/Lee/40, and B/Maryland 1/59 viruses. A single IV dose of peramivir was also effective against avian influenza virus in mice. Peramivir was modestly effective in completely immunocompromised mice (i.e., severe combined immunodeficient [SCID] mice). A single IV injection of peramivir was more effective than oseltamivir in ferrets and cynomolgus monkeys infected with B/Kadoma/1/2005 virus. In these animal studies, peramivir was effective when administered as a single IV dose either before or at the time of virus inoculation or up to 72 hours after inoculation.

Peramivir did not adversely affect certain immune system parameters in mice. Neither peramivir nor oseltamivir inhibited antibody production against influenza B in monkeys; treatment with both drugs was associated with decreased interleukin-6 (IL-6) production in influenza B-infected monkeys but did not affect tumor necrosis factor alpha (TNF-α) or monocyte/macrophage chemoattractant protein (MCP-1) production.

Reduced Susceptibility

The hemagglutinin (HA) and NA proteins of influenza A and B viruses interact with cellular receptors containing terminal neuraminic (sialic) acid residues. While HA binds to receptors and initiates viral infection, NA cleaves the receptors and liberates progeny virions. Because NA and HA surface proteins have a close functional relationship, reduced susceptibility to neuraminidase inhibitors can potentially arise through substitutions in either NA or HA. Amino acid substitutions in the NA have been shown to affect susceptibility of influenza viruses both in vitro and in vivo. In contrast, HA substitutions affect the susceptibility of influenza virus in vitro only. The Applicant considers HA substitutions generated in cell culture to be of less clinical significance than NA substitutions because the former affect the ability of the influenza virus to recognize the target receptors on cultured cells, which are believed to be different than those in the human respiratory tract.

In vitro studies investigating reduced peramivir susceptibility have included: 1) inhibition of NA activity, 2) sequencing of HA and NA genes, 3) generation of influenza A and B viruses with reduced in vitro drug susceptibility by passaging of virus in Madin-Darby canine kidney (MDCK) cells, and 4) reverse genetics to study the effects of site-specific NA substitutions in the homogenous genetic background on susceptibility. These studies identified viruses with substitutions in NA or HA alone, substitutions in both NA and HA, and deletions in RNA segment 6 that encodes for NA.

Resistance-associated gene substitutions in NA included an H275Y substitution in an influenza A/H1N1 virus, an R292K substitution in an influenza A/H3N2 virus, (b) (4) (b) (4) The influence of these NA substitutions on in vitro cross-resistance differed depending on the substitution. In general, the resistance profiles of peramivir, oseltamivir, and zanamivir differ for influenza A viruses, and to date, the majority of these viruses have been susceptible to at least one drug. All influenza B viruses with substitutions in the NA gene, whether isolated in the clinic or cell culture, are resistant to oseltamivir, but remain susceptible to either peramivir or zanamivir, with the exception of viruses with the (b) (4) substitution, which confers resistance to all three drugs.

- For influenza A/ H1N1 virus, the H275Y substitution causes resistance to OSE-C and intermediate susceptibility or resistance to peramivir depending upon virus genetic background, but susceptibility to zanamivir is retained. The R292K substitution causes resistance of influenza A/H3N2 to OSE-C and intermediate susceptibility to peramivir and zanamivir. Substitution at E119 in the N2 subtype generally confers resistance to zanamivir, while retaining susceptibility to oseltamivir and peramivir.

- For influenza B virus, the (b) (4) substitution causes resistance to OSE-C and peramivir, but retains susceptibility to zanamivir; substitution at D198 confers resistance to OSE-C, but retains sensitivity to peramivir and zanamivir; and substitution at (b) (4) confers resistance to all three drugs.

Substitutions in HA were selected in some cases in the absence of any resistance-associated substitutions in the NA. Importantly, the HA N63K and N145D substitutions conferred cross-resistance to both oseltamivir and zanamivir. These results are concerning as the use of the neuraminidase assay to screen for resistance would not be expected to detect resistance developing in the viral hemagglutinin. The HA G141E, D195N, and T197N substitutions, on the other hand, developed in earlier passage (passage 3) before the strain developed the NA H275Y substitution (passage 15). This observation is consistent with an earlier report for zanamivir where the HA substitutions appeared before the NA substitutions. A variant virus with no substitutions in the NA gene, but which had a HA substitution (K189E), was still susceptible to peramivir in vivo when mice were dosed orally with peramivir.

Peramivir was found to be effective in mice infected with influenza A/H1N1 virus with H275Y substitution in the NA gene, albeit at higher doses than required for wild type virus. Protection of mice by peramivir against lethal challenge with this virus was attributed to rapid absorption and high drug levels achieved with IM peramivir administration, and the less pronounced effect of the H275Y substitution on susceptibility to peramivir compared to oseltamivir. Some viral strains that were rendered less susceptible to peramivir by passage in MDCK cells in vitro were either similarly virulent or less virulent than wild type in adult mice or weanling mice.

Combination Therapy

Peramivir, when tested in combination with ribavirin, oseltamivir (or OSE-C), rimantadine, or favipiravir, generally showed additive or synergistic effects in vitro and in vivo against H3N2 and H1N1 strains. In the lethal influenza A virus mouse model, in addition to higher rates of survival, combination treatments resulted in improvements in other parameters (e.g., days to death, weight loss, oxygen saturation levels).

4.3 Preclinical Pharmacology/Toxicology

Please refer to Pharmacology-Toxicology Review by Dr. Kuei-Meng Wu for full details.

Peramivir has been evaluated in nonclinical studies following single- and/or repeat-dose in the mouse, rat, guinea pig, rabbit, dog, and cynomolgus monkey, first by the oral route, and subsequently by the IV and IM routes of administration. Following determination of (b) (4) the oral development program was terminated in favor of the parenteral formulations. The IM program was bridged to the IV program with conduct of one-month bridging studies in two species with agreement from FDA.

Toxicology studies with daily administration up to 28-31 days duration were conducted by the IM and IV (both bolus and continuous infusion) routes of administration in the rat

and monkey, as well as intravenous reproductive and developmental toxicity studies in the rat and rabbit. Chronic studies with IM dosing were conducted for 26 weeks in rats (biweekly dosing) and 52 weeks in monkeys (weekly dosing). In addition, studies evaluating genotoxicity and antigenicity were conducted. Two-week oral toxicity studies were conducted in juvenile rats and rabbits, a four-week IV toxicity study was conducted in juvenile rats, and several IV nephrotoxicity studies were conducted in rabbits. For the repeat-dose studies, parameters for evaluation included clinical observations, body weights, food consumption, hematology, coagulation, serum chemistry, urinalysis, ophthalmology, toxicokinetics, organ weights, and macroscopic and microscopic evaluation. As part of the oral development program, carcinogenicity studies were initiated in the rat and mouse and dosed to completion; however only the rat study was fully evaluated with complete histopathology.

In the rat, IV (bolus) doses up to 120 mg/kg/day for 28 days (mean area under the plasma concentration-time curve [AUC] $_{0–24}$ of 383,234 ng•hr /mL) and continuous infusions up to 1,440 mg/kg/day for one month (mean AUC_{0-24} up to 1,975 ng•hr /mL) were well tolerated. Similarly, in the monkey, bolus doses up to 90 mg/kg/day ($AUC_{0–24}$ of 541,580 ng•hr/mL) and continuous infusion doses up to 720 mg/kg/day ($AUC_{0–24}$ of 2,945 ng•hr /mL) for one month were well tolerated. Chronic studies in rats and monkeys with the IM route showed only injection site changes.

In the rabbit, following dosing from 1-9 days duration at IV doses ≥ 200 mg/kg/day, the kidney was identified as the target organ for toxicity, with increased BUN and creatinine and increased ratios of excreted sodium and chloride compared to creatinine. Microscopically, mild to marked acute tubular necrosis was observed which generally occurred at AUC values of > 1,130,000 ng•hr/mL. Several additional nephrotoxicity studies were conducted to more thoroughly evaluate these renal changes and all such studies were consistent in the identification of a no-observed-adverse-effect-level (NOAEL) of 100 mg/kg/day in the rabbit with respect to acute tubular necrosis. This renal toxicity was noted only in the rabbit and may have been related to the formation of the acyl glucuronide or other unidentified metabolite, which was not observed in other species or in humans.

Peramivir was not mutagenic or clastogenic in a battery of genotoxicity studies and did not alter reproductive or neonatal parameters nor was it teratogenic in the rat (up to 600 mg/kg) or rabbit (up to 200 mg/kg). Studies in rabbits demonstrated an increased rate of abortion and embryotoxicity with peramivir 200 mg/kg, but this was considered related to maternal nephrotoxicity; nephrotoxicity was also seen in nonpregnant rabbits. The maximum doses of peramivir administered to rats (600 mg/kg) and rabbits (200 mg/kg) were approximately 9-fold greater and 6-fold greater, respectively, than the 600 mg/day dose proposed in humans based upon body surface area. Therefore, the risk of fetal harm in humans due to peramivir exposure at the proposed single dose of 600 mg IV appears to be remote. Peramivir was not orally carcinogenic in rats.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology Review by Dr. Leslie Chinn for full details.

4.4.1 Mechanism of Action

Peramivir is a selective inhibitor of influenza viral neuraminidase.

4.4.2 Pharmacodynamics

Pharmacokinetic (PK) or pharmacodynamic (PD) correlates of clinical efficacy have not been established for influenza. Two studies of peramivir in the influenza mouse model suggested that the best predictor of efficacy was AUC, whether after oral or IV administration. To investigate the relationship between peramivir dose and potential metrics of clinical efficacy, such as plasma concentration above viral IC_{50} for a targeted duration of time, the Applicant developed a population PK/PD model, details of which are described here.

BCX1812-PPK-1

A population PK model for peramivir was developed using data from seven trials (0712T0611, 0714T0612, 0722T0621, 0815T0631, BCX1812-113, -212, and -311). A PD model was developed using studies BCX1812-212, 0722T0621 and 0815T0631, i.e. trials in acute uncomplicated influenza with paired subject-level data available for both time to alleviation of symptoms (TTAS) and peramivir IC_{50} values for baseline influenza virus clinical isolates. For PD modeling, the PK model was fixed, TTAS was described as a parametric hazard, and the relationship between plasma concentration and hazard of alleviation of symptoms was examined. The hazard was the sum of the baseline hazard and the drug effect (saturable function of the cumulative time above IC_{50}).

The Applicant's PK/PD modeling suggested that the effect of peramivir was dependent upon the duration that plasma drug concentration exceeded the IC_{50} for a given subject's virus isolate. In addition, the model showed that the relationship between duration above IC_{50} and hazard was saturable. A maximum effect (E_{max}) relationship was described and the time above IC_{50} that resulted in 50% (ET_{50}) of the maximum possible effect was reported as 21.8 hours.

For PD explorations related to safety, see Section 7.4.4 for results of the thorough QT study, BCX1812-106, and Section 7.5.1 for discussion of dose dependency for adverse events.

4.4.3 Pharmacokinetics

The PK of peramivir has been evaluated in an extensive clinical development program consisting of studies across all developmental phases, multiple routes of administration, and multiple subject populations. Studies BCX1812-113 and -111, conducted in healthy volunteers, established the bioequivalence of the IM and IV routes of administration of peramivir (see below).

The PK of peramivir is characterized by rapid and nearly complete absorption following IV/IM/SC administration, dose proportionality over a wide range of IV doses, distribution into the extracellular fluid spaces (including nose and throat), multi-exponential decline in plasma concentrations over time, and extensive clearance via the renal route of elimination. PK was noted to be similar between healthy subjects and subjects with influenza, as well as between Asian and U.S. populations.

Absorption

The peramivir dose-exposure relationship shows linearity and dose-proportionality over a wide range of peramivir doses. Following IV administration, the rate of entry of peramivir into the systemic circulation is dependent on the duration of infusion; in most trials, the duration of infusion was 15 to 30 minutes. Administration by IM or SC injection resulted in slower systemic absorption but with AUC values comparable to that of IV administration.

Distribution

Estimates of apparent volume of distribution indicate that peramivir is well distributed within the extracellular fluid compartment. Minor differences were observed in different study populations, depending on the PK methodology and the volume of distribution parameter being estimated, but only subtle differences with respect to ethnicity and gender were determined by population PK analyses. In human plasma, protein binding of peramivir was low (18-30%) and peramivir did not partition into red blood cells. Four trials (BCX1812-111, BCX1812-113, 0712T0611 and 0714T0612) showed that 3-9% of the peramivir plasma concentration was found in the nose and throat, and that concentrations > 2 ng/mL were present in these compartments for up to 24 hours post-dose following administration of peramivir IV doses ≥ 200 mg.

Metabolism

Peramivir did not appear to be a substrate or inhibitor of P-glycoprotein mediated transport, did not experience significant metabolism, and did not exhibit any interactions with cytochrome P450 (CYP) enzymes in either primary human hepatocytes or human liver microsomes, or with liver glucuronosyl transferase.

No metabolites of peramivir have been identified in either human urine or plasma. Unchanged peramivir was the only component identified in plasma and urine after single and multiple IV administrations in clinical trials. However, a pre-clinical in vitro study in human homogenates identified a metabolite of peramivir oxidized at the cyclopental ring at low concentrations (< 4% of added substrate); no other metabolites were found.

Elimination

Peramivir undergoes extensive renal elimination, with clearance paralleling that of glomerular filtration. With declining renal function there was no significant change in C_{max}, but the AUC of peramivir increased.

Following IV administration, concentrations of peramivir decline multi-exponentially, with an average effective half-life of approximately 3-8 hours (representing the major decline in peramivir concentrations over the initial 24 hours), and an average terminal half-life of approximately 20 hours. The estimates of mean peramivir systemic clearance for the IV doses from 300 to 1200 mg ranged from 6.03 to 6.78 L/hr in Japanese and U.S. Phase 1 trials; the overall weighted average value for systemic clearance across these trials was 6.62 L/hr. A cross-study comparison of peramivir systemic clearance indicated that there was no clinically relevant difference in the point estimate or variability in clearance across the wide range of peramivir doses utilized in the U.S. and Japanese trials.

Intrinsic Factors

Multiple population PK analyses performed at various stages of clinical development to investigate the effects of demographic factors (e.g., age, weight, gender, creatinine clearance, and ethnicity) on the PK of peramivir have revealed that, with the exception of renal function, there were no clinically relevant covariates that would influence exposure. Population PK results were consistent with results of the individual Phase 1 trials.

Bioequivalence of IM and IV Peramivir

Two Phase 1 trials have demonstrated comparable bioavailability between IM and IV administration of peramivir; these are described here:

Study BCX1812-113

This was a Phase 1 open-label, randomized, single-center, 2-period, cross-over trial to evaluate the relative bioavailability and safety of 600 mg peramivir administered IM versus 600 mg peramivir administered IV in healthy adult subjects. Single IV doses of peramivir were administered in one treatment period and single IM doses of peramivir were administered in the other treatment period.

Blood samples, nasal-wash and throat-gargle specimens were obtained at multiple time points up to 24 hours after administration of each dose in each treatment period for the evaluation of peramivir concentrations. A total of 24 subjects enrolled; 23 subjects were treated with IM peramivir and 24 subjects were treated with IV peramivir. Subjects were healthy males (54%) and females (46%) ranging in age from 22 to 61 years; mean (standard deviation) body mass index (BMI) at screening was 26.0 kg/m^2 (2.49 kg/m^2).

The 90% confidence interval (CI) for the geometric mean of the ratio of $AUC_{0-\infty}$ (IM) to $AUC_{0-\infty}$ (IV) at 24 hours was 97.7% to 103.5% and fell within the pre-specified bounds of 80% to 125%. Thus, the trial met its primary endpoint of demonstrating equivalence of the IM and IV formulations of peramivir. Bioequivalence was also demonstrated based on the secondary endpoints, AUC_{0-24} (CI: 97.6%, 103.5%) and $C_{24\ hr}$ (CI: 99.5%, 106.1%). The C_{max} was slightly higher with IV higher administration compared to IM, as would be expected, thus bioequivalence was not demonstrated by this criterion. The trial also demonstrated that IM and IV administration resulted in comparable concentrations of peramivir in nasal-wash and throat-gargle samples (although there were differences between the two compartments), with the IV formulation resulting in 6% and 48% of plasma concentration values being detected in the nose and throat, respectively, at 24 hours after administration.

Inspection of Study BCX1812-113 by the FDA Office of Scientific Investigations, Division of Bioequivalence and GLP Compliance determined that data generated by this trial were reliable and should be accepted for Agency review, thus permitting use of the peramivir IM clinical trial data in support of this application.

Study BCX1812-111

This was a Phase 1 open-label, single-dose, single-center, treatment sequence-randomized, parallel-group trial to evaluate the PK, bioavailability and safety of IM peramivir administered to healthy adult subjects. Subjects were sequentially allocated to 3 cohorts of 9 subjects each. In parallel, subjects in each of the 3 cohorts received single doses of peramivir on Days 1, 8, and 15; Cohort 1 received peramivir 75 mg, Cohort 2 received peramivir 150 mg, and Cohort 3 received peramivir 300 mg. Within each cohort, peramivir was administered as 3 different treatments, as follows: Treatment A: peramivir by IV infusion; Treatment B: peramivir by IM injection(s); Treatment C: peramivir by IM injection(s) with co-administration (± 5 min) of 1 g oral probenecid. Subjects within each cohort were randomized to receive the 3 treatments according to 1 of 3 sequences: ABC, BCA, or CAB. In this trial, IV infusions were administered over a period of 15 minutes.

The trial enrolled 24 male and 4 female subjects ranging in age from 19 to 57 years. Of the 27 subjects enrolled, 24 (89%) completed all study requirements; one subject in each cohort withdrew participation prior to completing all study assessments.

The PK results showed that the absolute bioavailability of the IM formulation was high (92% to 99% across treatment groups) and that increase in peramivir overall exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$) was dose proportional following both IV and IM administration. Increases in C_{max} were approximately dose-proportional, with peak concentrations slightly lower for an IM injection compared to a 15-minute IV infusion. Renal clearance accounted for >90% of total clearance, although drug recovery was not complete in the 72-hr urine collection period; total clearance correlated well with creatinine clearance values and was independent of the dose administered. A single dose of 1 g oral probenecid had negligible effect on the PK of IM peramivir, consistent with lack of active renal tubular secretion or re-absorption of peramivir. Lastly, following single doses of peramivir administered either IV or IM, concentrations of peramivir (corrected for dilution) were detectable for up to 24 hours in nasal-wash and throat-gargle samples; the concentrations were generally seen to increase over time, suggesting a slightly delayed clearance of drug at these anatomic sites, in comparison to plasma.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

BioCryst and its partner Shionogi completed ten Phase 2 or 3 clinical trials to evaluate the efficacy and safety of peramivir in the treatment of influenza (Table 2). Seven trials enrolled subjects with acute uncomplicated influenza; the remaining three were conducted in subjects hospitalized with influenza. All trials were submitted for review as part of this application.

Table 2: Summary of Phase 2 and 3 Clinical Trials of Peramivir

Study ID	Population	Study Design	Peramivir Dosage	# Subjects Randomized/Treated	Role in NDA
Phase 2/3 Trials in Acute Uncomplicated Influenza – Placebo-Controlled					
0722T0621	Adults with uncomplicated acute influenza	Phase 2 double-blind, placebo-controlled, parallel group, comparative dose-finding	300 mg or 600 mg IV single dose	Peramivir 300 mg IV 99/99 Peramivir 600 mg IV 100/99 Placebo 101/100	Pivotal

BCX1812-211	Same as above	Phase 2 randomized, double-blind, placebo-controlled	150 mg or 300 mg IM single dose	Peramivir 150 mg IM 114/113 Peramivir 300 mg IM 115/115 Placebo 115/114	Supportive
BCX1812-311	Same as above	Phase 3 randomized, double-blind, placebo-controlled	300 mg IM single dose	Peramivir 300 mg IM 57/57 Placebo 25/25	Supportive
BCX1812-212	Same as above	Phase 2 randomized, double-blind, placebo-controlled	600 mg IM single dose	Peramivir 600 mg IM 202/200 Placebo 203/202	Supportive
Phase 3 Trials in Acute Uncomplicated Influenza – Non-Placebo Controlled					
0815T0631	Adults with uncomplicated acute influenza	Phase 3 randomized, double-blind, oseltamivir-controlled	300 mg or 600 mg IV single dose	Peramivir 300 mg IV 366/363 Peramivir 600 mg IV 368/365 Oseltamivir 365/365	Informative
0816T0632	Adults with influenza and high-risk factors	Phase 3 randomized, double-blind, non-controlled	300 mg or 600 mg IV for 1 to 5 days	Peramivir 300 mg IV 21/21 Peramivir 600 mg IV 21/21	Informative
Phase 2/3 Trials in Hospitalized Patients with Influenza					
BCX1812-201	Hospitalized adults with acute serious or potentially life-threatening influenza	Phase 2 randomized, double-blind, oseltamivir-controlled	200 mg or 400 mg IV QD for 5 days	Peramivir 200 mg IV 45/45 Peramivir 400 mg IV 46/46 Oseltamivir 46/46	Informative
BCX1812-301	Hospitalized adults, adolescents, and children with influenza [a]	Phase 3 randomized, double-blind, placebo-controlled, add on to standard of care	600 mg IV QD for 5 or 10 days	Peramivir 600 mg IV 268/264 Placebo 137/134	Informative
BCX1812-303	Hospitalized adults, adolescents, and children with	Phase 3 randomized, open-label	600 mg IV QD or 300 mg IV BID for 5 or 10	Peramivir 600 mg IV 117/115 Peramivir 300 mg IV	Informative

	confirmed or suspected influenza [a]		days	117/115	
Pediatric Trials					
0918T0633	Children (≥ 28 days to <16 years) with influenza	Phase 3 open-label, single-arm	10 mg/kg (max 600 mg) IV QD for 1 to 5 days	117/117	Informative

Abbreviations: BID = twice daily; QD = once daily; IM = intramuscular; IV = intravenous
a) Adults were defined as ≥ 18 years of age, adolescents >12 to <18 years of age, and children ≥ 6 to <12 years of age.

5.2 Review Strategy

Because the indication under consideration was the treatment of acute uncomplicated influenza in adults, the clinical review for this application was based primarily on data from the four placebo-controlled Phase 2 or 3 trials in adults with acute uncomplicated influenza, namely Studies 0722T0621, BCX1812-211, BCX1812-212, and BCX1812-311.

This reviewer performed the analyses of safety for the proposed indication using these four trials as the basis. In addition, pooled analyses of safety were conducted for submission-specific events of interest by pooling data for the 300 mg and 600 mg peramivir doses from these four trials plus the oseltamivir-controlled trial in adults (Study 0815T0631) and comparing them to pooled safety data from a cohort of placebo-treated subjects. For the integrated analyses of safety, primary safety data from all Phase 2/3 trials, safety summaries from Phase 1 trials in healthy volunteers, and postmarketing data from foreign sources were also reviewed. The following review tools were used by this reviewer to perform the analyses of safety: JReview®, Integrated Clinical Systems, Inc. (Version 9.2.5); JMP®, SAS Institute Inc. (Version 10); and the MedDRA-based Adverse Event Diagnostic Tool (MAED), developed by the FDA (Version 1.0).

The analysis of efficacy was conducted in collaboration with Dr. Thomas Hammerstrom, Biometrics, and based primarily on data from the Shionogi Study 0722T0621, with supplemental data from other controlled trials of peramivir in acute uncomplicated influenza, namely Studies BCX1812-211, -212, -311, and 0815T0631. For the analyses of efficacy, this review used JMP software and limited the analyses to the four placebo-controlled trials.

Dr. Leslie Chinn, Clinical Pharmacology, reviewed the Phase 1 Studies BCX1812-111 and -113, which demonstrated the bioequivalence of the IM and IV peramivir formulations. Dr. Chinn also reviewed the other Phase 1 clinical pharmacology data submitted in this NDA package, including results from a thorough QT study (Study

BCX1812-106), and conducted dose-response analyses of the Phase 2/3 trials. Antiviral activity and available resistance data from the Phase 2/3 trials were reviewed by Dr. Takashi Komatsu, Virology.

5.3 Discussion of Individual Studies/Clinical Trials

The pivotal trial supporting the use of IV peramivir for the proposed indication was Study 0722T0621, a Phase 2 single dose trial that enrolled 300 Japanese adult subjects with confirmed influenza and evaluated two doses of IV peramivir (300 mg and 600 mg).

Studies BCX1812-211, BCX1812-212, and BCX1812-311 provided supportive data for the use of single parenteral doses of peramivir to treat acute influenza in an outpatient setting. In these trials, peramivir at doses ranging from 150 mg to 600 mg was administered as a single dose via bilateral IM gluteal injections. As noted previously, bioequivalence of the IM and IV peramivir formulations was demonstrated in Phase 1 Studies BCX1812-111 and BCX1812-113 (see Section 4.4.3), thus permitting use of the IM data in support of this application.

All of four of these trials were randomized, double-blind and placebo-controlled trials that used the same clinical endpoint as the primary measure of efficacy, namely time to alleviation of symptoms (TTAS). This endpoint was previously established as suitable for clinical trials of acute uncomplicated influenza in the FDA guidance for industry *Influenza: Developing Drugs for Treatment and/or Prophylaxis*.[10] Further, all four of the trials used the same seven symptoms for the TTAS composite endpoint (nasal congestion, sore throat, cough, aches and pains, fatigue (tiredness), headache, feeling feverish), which were similar to those used in the registrational trials of Tamiflu (oseltamivir phosphate) and Relenza (zanamivir). Each trial followed subjects for at least 14 days post-dosing and required that subjects record the severity of their symptoms twice daily through Day 9 and then once daily from Days 10-14 in diary cards. Subjects were instructed to record the severity of each symptom at the time of completing the diary entry, and not their worse score over the previous 12-24 hours. In each trial, self-assessment of temperature was collected on diary cards twice daily for 14 days. Further, in each trial the TTAS endpoint required that all symptoms be no more than mild and that alleviation of symptoms be sustained for a minimum of 21.5 hours. Each of these four Phase 2/3 placebo-controlled trials is described in further detail below

The other two Phase 3 trials in subjects with acute uncomplicated influenza (Studies 0815T0631 and 0816T0632) are also described here. Because the efficacy of available influenza treatment is modest, variable, and cannot be predicted well enough to support an adequate noninferiority margin, the comparative trial of peramivir and oseltamivir in adult subjects with acute uncomplicated influenza (Study 0815T0631) was not relied

[10] FDA guidance for industry, 2011, Influenza: Developing Drugs for Treatment and/or Prophylaxis

upon to a great extent to assess the efficacy of peramivir, but this trial was used to provide additional information regarding the drug's antiviral activity and safety.

The trials in high-risk (Study 0816T0632) and hospitalized subjects (Studies BCX1812-201, -301, and -303), on the other hand, evaluated a different population than the one targeted in the proposed indication and largely used different treatment dosages than the single dose proposed in this application. Study designs in these trials also differed, and some were not controlled. Furthermore, clinical data from these trials were often confounded by underlying comorbidities, severity of influenza illness, or use of concomitant medications, and therefore did not allow for as clear an assessment of peramivir compared to the controlled trials in acute uncomplicated influenza. Therefore, these trials were not reviewed in great detail except where pertinent to the overall assessment of peramivir safety. Synopses (study designs and reported results) of these trials are provided below; the hospitalized trials in particular are described because inclusion of this information is proposed in draft labeling, as discussed in the pre-submission meetings with FDA (see Section 2.5).

The Phase 3 Japanese pediatric trial (Study 0918T0633) is reviewed in Section 7.6.3.

Placebo-Controlled Clinical Trials in Acute Uncomplicated Influenza

Study 0722T0621
Phase II Clinical Study of Single-Dose Intravenous Peramivir in Patients with Influenza Virus Infection - A Double-Blind, Parallel Group, Comparative Dose-Finding Study

This was a Phase 2 multicenter, placebo-controlled, double-blind, parallel-design trial conducted in Japan in adult subjects with acute uncomplicated influenza. The objective was to evaluate the efficacy, dose-response relationship and safety of IV peramivir administered as a single dose. Up to 300 subjects were planned for enrollment across 75 Japanese sites during the 2007-2008 influenza season. Subjects were randomized 1:1:1 to peramivir 300 mg IV, peramivir 600 mg IV, or placebo. Randomization was stratified by current smoking status and composite influenza symptom score at baseline.

Main eligibility criteria were:

- Age 20-65 years old
- Inpatient or outpatient
- Fever of ≥ 38.0°C (axillary temperature) with no clinical findings of bacterial infection or any other non-influenza cause (e.g., drug reactions)
- At least two of the following symptoms due to influenza of moderate or greater severity:
    - Systemic symptoms: headache, aches and pains of the muscle or joints, feverishness or chills, fatigue
    - Respiratory tract symptoms: cough, sore throat, and nasal congestion

- Time from onset of illness no more than 48 hours (at the time of enrollment), defined as either:
    - the time when temperature was first measured as elevated (by at least 1°C above the subject's own normal temperature), or
    - the time when subject experienced at least two systemic symptoms or respiratory tract symptoms of influenza
- A positive rapid antigen test (RAT) for influenza performed with a nasal or throat swab specimen.

Individuals with the following were excluded:

- Respiratory disease requiring oxygen use
- Convulsions or other neurological symptoms,
- Chronic obstructive pulmonary disease (COPD)
- History of congestive heart failure requiring pharmacotherapy (New York Heart Association [NYHA] Functional Class II, III, or IV within the previous 12 months)
- Renal impairment requiring hemodialysis or known or suspected concurrent renal impairment that is moderate or severe
- ECG findings that suggest clinically significant ischemic heart disease or serious arrhythmia
- Screening ECG showing QTc ≥480 msec or bradycardia (heart rate: < 40 beats/minute)
- Currently on immunosuppressive treatments or has an immunodeficiency disorder (e.g., poorly controlled diabetes mellitus or HIV infection)
- Complications of concurrent infection requiring antimicrobial drugs (excluding skin infections)
- Use of oseltamivir phosphate (Tamiflu®), zanamivir hydrate (Relenza®) or amantadine hydrochloride (Symmetrel®) within the past seven days
- Direct family member who experienced sudden death
- Clinically significant disorder that requires hospitalization such as cardiovascular, central nervous or metabolic (thyroid function, adrenal function) disorder, cancer, hepatitis or liver cirrhosis
- History of hypersensitivity, allergy or serious adverse drug reaction possibly attributable to oseltamivir phosphate, zanamivir hydrate or amantadine hydrochloride
- History of hypersensitivity, allergy or serious adverse drug reaction possibly attributable to acetaminophen
- Pregnancy, suspected pregnancy, or positive urine pregnancy test
- Breastfeeding
- Received any other investigational drug within the past 3 months (90 days)

Prohibited medications included antiviral drugs, antimicrobial or antifungal agents (except topical preparations), non-steroidal anti-inflammatory drugs (NSAIDs), antitussives or expectorants, combination cold remedies, antihistamines, corticosteroids

(except topical preparations), immunosuppressants, Chinese herbal medicines indicated for influenza virus infection, drugs with potential risk of prolonging QTc, and other investigational drugs.

Study duration was 14 days. Subjects were seen in clinic on Days 1, 2, 3, 5, 9, and 14. All subjects were treated via intravenous infusion over a period of 30 minutes using the investigational drug product allocated on Day 1.

Throat swabs and nasal swabs (one-sided) were collected at the time of screening and during visits on Days 2, 3, 5 and 9 for influenza viral culture and quantitative polymerase chain reaction (PCR) assay. These specimens were used to evaluate virus subtype classification (A-H1/H3/H5, B), NA inhibition activity (inhibitory concentration$_{50}$ [IC_{50}]), and virus titers (tissue culture infective dose$_{50}$ [$TCID_{50}$]). Blood samples for influenza virus Type A and Type B serum antibody titers were also collected at the time of screening and at the completion of study (Day 14). Blood samples to evaluate levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) were collected at the time of screening, during visits at Days 2, 3 and 5 and at the completion of study (Day 14) or discontinuation.

Blood samples for plasma concentration measurements were collected immediately before completion of the IV infusion on Day 1 and at one time point each during Day 2 (if possible) and Day 3, and also after completion of the IV infusion on Day 1 whenever feasible. Further, for some subjects, blood samples were collected 30 minutes after the start of dosing (immediately prior to the end of the IV infusion), and at 1, 2, 4, 6, 8, 12, 24 and 48 hours after the start of dosing.

Subjects were asked to self-evaluate their influenza symptoms twice a day (in the morning and at night) from the time of screening until Day 9, and then once a day from Day 10 to 14, recording the results in a patient diary. The diary contained definitions for symptom scores using a 4-point scale [0: no symptoms (normal condition); 1: mild symptoms (mildly uncomfortable); 2: moderate symptoms (very uncomfortable); and 3: severe symptoms (unbearable)]. Subjects were asked to record the severity of each symptom at the time of completing the entry, and not rate their worse score over the preceding 12-24 hours.

Axillary temperatures were measured and recorded twice daily every 12 hours in the diary up to Day 14; resolution of temperature was defined as < 37.0°C maintained for at least 12 hours. Body temperature measurements were performed either prior to or after at least 4 hours after the most recent use of an antipyretic agent.

Subjects were also asked to evaluate their ability to perform daily activities using a Visual Analogue Scale (0 - 10) once a day from the time of screening until Day 14, recording their results in the patient diary.

Concomitant use of acetaminophen was allowed for relief of severe influenza symptoms such as fever, headache and myalgias. If acetaminophen was used, the subject was to record the doses taken and times of medication in the patient diary.

Safety evaluations included physical examinations, vital signs and assessment of adverse events (AEs) at each clinic visit; electrocardiograms (ECGs) at Screening, post-infusion on Day 1, and on Days 3 and 14; and pregnancy tests (urinary hCG) at Screening and Day 14. Treatment-emergent AEs were defined as those occurring from the start of study drug administration to the completion of Visit 6 (Day 14) or discontinuation from study; AEs were graded according to the Division of AIDS (DAIDS) AE grading table.

Safety laboratory tests were collected at Screening and Days 3 and 14 and consisted of the following tests:

Category	Test items
Hematology	WBC count, RBC count, hemoglobin, hematocrit, differential leukocyte count, and platelet count
Blood biochemistry	AST, ALT, LDH, ALP, CK, total bilirubin, direct bilirubin, total protein, albumin, BUN, serum creatinine, uric acid and glucose
Electrolytes	Na, K, Cl, Mg, Ca, P
Urinalysis	Bilirubin (qualitative), protein (qualitative), glucose (qualitative), ketones (qualitative), urobilinogen (qualitative), occult blood (qualitative), urine sediment (red cells, white cells), NAG, β2-microglobulin, α1- microglobulin, and urinary albumin

The primary efficacy endpoint was TTAS, defined as the time from the start of study drug infusion to the timepoint where influenza symptoms disappeared. The term disappearance of influenza symptoms was defined as the timepoint where all seven of the influenza symptoms had become “0: none” or “1: mild” and such state persisted for at least 21.5 hours (24 hours minus 10%) according to the patient diary.

Secondary efficacy endpoints were as follow:

- Amount of change in the composite influenza symptoms score from baseline at 24, 36, 48 and 96 hours after dosing
- Time to recovery to normal temperature
- Amount of change in virus titer per unit time
- Time to resumption of daily activities
- Amount of change in IL-6 and TNF-α per unit time
- Changes in drug sensitivity (i.e., development of resistance)
- Amount of acetaminophen used
- Incidence of influenza complications (sinusitis, bronchitis, otitis media, pneumonia)

The safety endpoint was the incidence of AEs and adverse drug reactions (ADRs). PK endpoints included the plasma concentration of the drug (unchanged form) at various timepoints.

The sample size of 300 subjects was based on the assumption that the median TTAS would be 137 hours for the placebo group (based on previous clinical study reports). A median TTAS of 87 hours was anticipated for both the peramivir 300 mg and 600 mg groups. Assuming the TTAS was exponentially distributed and adopting a statistical one-sided significance level of 0.025, a power of 0.80, a follow-up period of 336 hours (14 days), and the log rank test for statistical testing, the required number of subjects was calculated to be 67 per treatment group. Eighty (80) subjects per group (total 240 subjects) were planned in case of an imbalance in allocation and to account for cases not verified to be influenza. A maximum of 300 subjects was allowed to enhance the precision of the efficacy evaluation and to gather more safety data.

There were no changes made to the protocol with respect to study procedures or methods of assessment. The "Statistical Analysis Protocol" (Version 1) was prepared on February 29, 2008, and was revised on June 2, 2008 (Version 2). The primary modification involved converting the measurement units used in analysis of change in the virus titer per unit time and change in the virus titer from log10 ($TCID_{50}$/25 µL) to log10 ($TCID_{50}$/mL). Comparison of the incidence of the clinical and laboratory-related AEs and ADRs was also added to the safety assessment.

Study BCX1812-211
A Phase II, Multicenter, Randomized, Double-Mask, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza

This was a Phase 2 multinational, randomized, double-mask trial comparing the efficacy and safety of peramivir IM versus placebo in adults with uncomplicated acute influenza. Three hundred (300) subjects were planned for enrollment across 151 clinical study sites in seven countries in both the Northern and Southern hemispheres (United States, Canada, United Kingdom, Australia, Hong Kong, New Zealand, and South Africa) from January through September, 2007. Subjects were stratified according to their current smoking behavior and centrally randomized 1:1:1 to receive one of three treatments: peramivir 150 mg IM, peramivir 300 mg IM, or placebo. Study drug was administered as one 2-mL IM injection in each gluteal muscle (total of 4 mL injected in divided doses).

The objectives, endpoints, study procedures, and sample size considerations were similar to those described for Study 0722T0621.The date of the original protocol was October 27, 2006. There were subsequently four amendments to the protocol, some of which differentiated it from Study 0722T0621. These differences included:

- No upper age limit for inclusion

- The use of oral (instead of axillary) temperature measurements
- The presence of fever at time of screening requirement could be waived if subjects had a history of fever in the 24 hours prior to Screening and had been administered antipyretic(s) in the 6 hours before Screening. This inclusion criterion was further modified in Amendment 4 (June 28, 2007) to allow enrollment of subjects who described the presence of the symptom of feverishness in the 48 hour period before Screening without a history of documented temperature elevation during the 48 hour period prior to Screening.
- Subjects with severe COPD were excluded, but subjects with COPD of mild or moderate severity could be included
- The use of certain anticoagulants was added as an exclusion criterion because study drug was to be administered IM
- The Day 2 and Day 3 visits could occur at the subject's home rather than in the clinic if the procedures at such visits could be conducted by appropriately trained personnel
- ECGs were performed only at Screening
- Expectorants and/or throat lozenges were allowed during the trial
- Daily self-assessment of injection sites for any discomfort was added to the patient diary card (for the first 5 days)
- Urinalysis included dipstick tests for protein, glucose, ketones, blood, urobilinogen, nitrite, pH, and specific gravity and microscopic evaluation for RBCs and WBCs. Any positive test for protein by dipstick test (trace + or higher) required a follow-up 24 hour urine collection for assessment of protein. Urine protein electrophoresis (UPEP) was to be performed if the 24-hour urine test yielded total protein >150mg/24 hours.
- A Data Monitoring Committee (DMC) was added for review of safety data.

Study BCX1812-311
A Phase 3 Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza - The IMPROVE 1 Study *(**I**ntra**M**uscular **P**eramivir for the **R**elief **O**f symptoms and **V**irologic **E**fficacy)*

This was a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the 300 mg dose of IM peramivir versus placebo in adults with uncomplicated influenza. Subjects were randomized 2:1 to peramivir or placebo; randomization was stratified according to smoking status and RAT test result for influenza A or B. Because data from the Phase 2 trial of IM peramivir suggested that peramivir was less active against influenza B infections, a sample size of 600 subjects was planned to allow for a sufficient number of subjects with evidence of influenza A infection to achieve study power. The study objectives, endpoints, procedures and eligibility criteria were otherwise nearly identical to those for Study BCX1812-211

Study BCX1812-311 was planned as a multinational, multicenter trial beginning in January 2008; however, the trial was terminated by BioCryst after only 82 subjects were enrolled. The reason for study termination was to focus development efforts on a more concentrated formulation which would allow for evaluation of higher IM doses. At the time of study termination, 37 sites in the United States had enrolled subjects. The last subject completed study on February 15, 2008.

Study BCX1812-212
A Phase II, Multicenter, Randomized, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir 600 mg in Subjects with Uncomplicated Acute Influenza

This was a Phase 2 multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of a single dose of peramivir 600 mg (administered as two bilateral 2-mL IM injections of 300 mg) versus placebo in adults with uncomplicated acute influenza. Approximately 320 subjects were planned to be randomized across 66 sites in four countries (United States, South Africa, Australia, and New Zealand) during the 2008-2009 influenza season. Subjects were centrally randomized in a 1:1 ratio to peramivir 600 mg IM or placebo. The sample size of 320 subjects was selected to allow for enrollment of a minimum of 252 subjects with influenza A (by PCR) and up to 50 subjects with influenza B (determined by RAT at enrollment). The study objectives, endpoints, procedures and eligibility criteria for this trial were similar to those of Studies BCX1812-211 and -311. Notable differences were (1) the inclusion criterion that the onset of symptoms could not be more than 36 hours before presentation and (2) samples for viral cultures were not collected on Days 2 or 5, but were collected on Day 4. Importantly, Study BCX1812-212 was conducted during an influenza season in which the dominant circulating strain of influenza A/H1N1 virus had the NA H275Y substitution, which resulted in reduced susceptibility to neuraminidase inhibitors.

Table 3 provides a comparison of the primary and secondary efficacy endpoints across the four placebo-controlled trials of peramivir for the acute uncomplicated influenza indication.

Table 3: Comparison of Efficacy Endpoints across the Placebo-Controlled Trials of Peramivir in Acute Uncomplicated Influenza

Endpoints	0722T0621	BCX1812-211	BCX1812-311	BCX1812-212
Time to alleviation of symptoms[a]	Primary	Primary	Primary	Primary
Time to resolution of fever[b]	Secondary	Secondary	Secondary	Exploratory
Change in influenza virus titer by $\log_{10}$ $TCID_{50}$/mL and by RT-PCR[c]	Secondary	Secondary	Secondary	Secondary
Time-weighted change from Baseline in $TCID_{50}$/mL	–	Secondary	Secondary	Secondary
Time to resumption of usual daily activities[d]	Secondary	Secondary	Secondary	–
Incidence of influenza-related complications	Secondary	–	Secondary	Exploratory
Change from Baseline in composite influenza symptom score	Secondary	–	–	Exploratory
Change from Baseline in IL-6 and TNFα	Secondary	–	–	–
Changes in drug sensitivity[e]	Secondary	–	Exploratory	Exploratory
Amount of antipyretic/acetaminophen used	Secondary	–	–	–
Percentage of subjects shedding virus[f]	–	–	–	Secondary

Abbreviations: IL-6 = interleukin-6; RT-PCR = reverse transcriptase polymerase chain reaction; $TCID_{50}$ = tissue culture infective $dose_{50}$; TNFα = tumor necrosis factor alpha.
Source: Adapted from Table 1 of Integrated Summary of Efficacy (ISE), page 23

Oseltamivir-Controlled Clinical Trials in Acute Uncomplicated Influenza

Study 0815T0631
A Phase III Clinical Study of Single-Dose Intravenous Peramivir in Patients with Influenza Virus Infection: A Double-Blind, Parallel Group, Comparative Study with Oseltamivir Phosphate

This was a Phase 3 double-blind, parallel group, comparative trial of single-dose IV peramivir in adult subjects with acute uncomplicated influenza. The objective was to assess the non-inferiority of single-dose IV peramivir 300 mg and 600 mg compared with oral oseltamivir phosphate 75 mg given orally twice daily for 5 days. A total of 1,099 subjects were enrolled across 146 sites in Japan, South Korea and Taiwan during the 2008-2009 influenza season. Subjects were enrolled within 48 hours of symptoms onset. Study drug was administered once by intravenous drip infusion over 15 to 60 minutes in this trial. Clinical efficacy evaluations included subject self-assessments of influenza symptoms and body temperature from Screening to Day 14. Virology efficacy assessments included nasal and pharyngeal swabs. The primary endpoint was TTAS as defined in Study 0722T0621. The predefined non-inferiority margin was established as 17%, based on a meta-analysis of efficacy from the placebo-controlled registrational trials of Tamiflu. Similar to Study BCX1812-212, this trial was conducted during a season in which the predominant circulating influenza strain was an influenza A/H1N1 virus that contained an H275Y substitution. This substitution resulted in reduced

susceptibility to oseltamivir and peramivir compared to wild type virus. This issue notwithstanding, the trial met its primary endpoint. The median TTAS was 78 hours in the peramivir 300 mg group, 81 hours in the peramivir 600 mg group, and 81.8 hours in the oseltamivir group. In both the peramivir 300 mg and 600 mg groups, the upper limits of the 97.5% CI for the hazard ratio to the oseltamivir group were below the predefined non-inferiority margin. Safety results from this trial are discussed in Section 7.

Uncontrolled Clinical Trials in Acute Uncomplicated Influenza

Study 0816T0632
A Phase III Clinical Study of Intravenous Peramivir in Patients with Influenza Virus Infection: A Study in Patients with High-Risk Factors

This was Phase 3, double-blind, non-controlled, multicenter trial conducted in Japan of IV peramivir administered once daily for 1 to 5 days in subjects with influenza and high-risk factors. High-risk factors included poorly controlled diabetes, chronic respiratory disease undergoing pharmacotherapy, or use of drugs that may suppress immune function (e.g., oral or inhaled adrenocortical steroids, immunosuppressant agents [excluding tacrolimus]). A total of 42 subjects were enrolled across 37 sites from January to May, 2009. Subjects were administered IV peramivir at a dose of 300 mg (N=21 randomized) or 600 mg (N=21 randomized). Study drug was administered immediately after enrollment on Day 1. On subsequent days, study drug was continued at the discretion of the investigator based on body temperature ≥ 37.5°C or clinical manifestations. (Within the safety analysis set, 88.1% of the subjects received either 1 or 2 doses of study drug.) Clinical efficacy evaluations included subject self-assessments of body temperature, influenza symptoms, and daily activity. These were assessed daily from Screening to Day 14 and recorded in a patient diary. The primary endpoint was TTAS as previously defined for the other peramivir trials of acute uncomplicated influenza; however, no statistical testing was performed for the primary endpoint. In the per-protocol-set, the median TTAS was 114.4 hours for the peramivir 300 mg group (N=18) and 42.3 hours for the peramivir 600 mg group (N=19). Major safety results from this trial are discussed in Section 7.2.

Clinical Trials in Hospitalized Patients with Influenza

Study BCX1812-201
A Phase 2, Multicenter, Randomized, Double-Mask, Double-Dummy Study Comparing the Efficacy and Safety of Peramivir Administered Intravenously Once Daily versus Oseltamivir Administered Orally Twice Daily in Adults with Acute Serious or Potentially Life-Threatening Influenza

This was multinational, randomized, double-masked, double-dummy trial to compare the efficacy and safety of IV peramivir administered once daily (QD) for 5 days versus oseltamivir 75 mg (oral suspension) administered twice daily (BID) for 5 days in

hospitalized adults with acute serious or potentially life-threatening influenza. Although not indicated for the treatment of hospitalized patients with influenza, oseltamivir was chosen as the active comparator because it is generally considered the drug of choice for first-line influenza therapy. Subjects with signs and symptoms compatible with acute influenza infection (present for no more than 72 hours) and positive RAT or other similar test results were enrolled. Criteria for hospitalization included: age ≥ 60 years, history of cardiac or pulmonary disease, presence of diabetes, oxygen saturation < 94% or systolic blood pressure < 90 mmHg. A subject without any of these criteria could still be enrolled if in the investigator's opinion hospitalization was indicated for supportive care. Enrollment was stratified according to duration of influenza symptoms and oxygen saturation at screening. Subjects were randomized to receive 1 of 3 treatments: peramivir 200 mg or 400 mg administered IV QD for 5 days (5 doses) or oseltamivir 75 mg oral suspension administered orally BID for 5 days (10 doses). The primary efficacy endpoint was time to clinical stability, defined as normalization of at least 4 of the 5 following signs: temperature ≤ 37.2^{o}C oral, oxygen saturation ≥ 92%, respiration rate ≤ 24/minute, heart rate ≤ 100/minute, and systemic blood pressure ≥ 90 mmHg. Subjects were evaluated at least twice daily while hospitalized to assess for clinical stability.

Medical Officer's Comment:
No clinical endpoints have been validated thus far for clinical trials of hospitalized patients with influenza. The primary endpoint used in Study BCX1812-201, i.e. time to clinical resolution, was an unvalidated endpoint derived from a similar endpoint in clinical studies of community-acquired pneumonia. This endpoint was agreed upon by FDA reviewers; however, no previous well-controlled trial of neuraminidase inhibitors in hospitalized patients has used an objective clinical endpoint similar to the one described here.

A total 137 subjects were enrolled across 43 centers in 7 countries (United States, Canada, Australia, New Zealand, South Africa, Hong Kong, and Singapore) from July 2007 to September 2008. A total of 91 subjects were treated with peramivir (200 mg N=45, 400 mg N=46) and 46 subjects were treated with oseltamivir.

Descriptive statistical methods were used to summarize the trial data, with hypothesis testing for the primary and selected secondary efficacy endpoints. Among the 122 subjects with confirmed influenza included in the primary efficacy analysis, the median time to clinical stability was 23.7 hours in the peramivir 200 mg group, 37.0 hours in the peramivir 400 mg group, and 28.1 hours in the oseltamivir group. In a post-hoc subgroup analysis of subjects not clinically stable at enrollment (N=97), the median time (95% CI) to clinical stability was 31.0 hours (17.2, 47.7) with peramivir 200 mg treatment, 24.3 hours (21.2, 47.5) with peramivir 400 mg treatment, and 35.5 hours (23.3, 37.9) with oseltamivir treatment. Peramivir and oseltamivir were similarly effective with respect to other secondary clinical efficacy endpoints, including incidence of clinical relapse, time to hospital discharge, change from baseline CXR, and mortality. (No

clinical relapses or deaths occurred among patients with confirmed influenza in this trial.) The median time to resumption of ability to perform usual activities was approximately 4 days shorter for subjects treated with either dose of peramivir compared to oseltamivir; this was the only clinical endpoint that showed a meaningful difference between the three treatment groups.

Quantitative assessments of virus shedding in nasopharyngeal specimens showed rapid decreases over the first 48 hours of treatment in most subjects. Decreases in influenza A virus titers were similar among the three treatments. In contrast, decreases in influenza B virus titers were numerically greater at each time point in subjects treated with peramivir compared with subjects treated with oseltamivir, and decreases in titer were dose-ordered at each time point, suggesting a possible plateau of the dose-response relationship. However, the number of subjects with culture-positive influenza B infection (N=32) was relatively small compared with the number of subjects with influenza A, and was not balanced between treatment groups. Only 6 subjects with influenza B were randomized to peramivir 400 mg, for example.

Safety outcomes were relatively similar between the three treatment groups. The most common treatment-emergent AEs (TEAEs) in each group were diarrhea (11% peramivir 200 mg, 15% peramivir 400 mg, 2% oseltamivir), nausea (4% peramivir 200 mg, 11% peramivir 400 mg, 9% oseltamivir), and hypokalemia (7% peramivir 200 mg, 9% peramivir 400 mg, 11% oseltamivir). There were 18 serious AEs (SAEs) reported in 14 subjects. Two SAEs were judged as possibly related to study treatment – severe diarrhea in a subject receiving peramivir 400 mg and angioedema in a subject receiving oseltamivir. Three subjects were withdrawn as a result of a TEAE. One subject treated with peramivir 200 mg was withdrawn because of anxiety and altered mood, and one subject treated with peramivir 400 mg was withdrawn because of an SAE of acute respiratory failure. One subject assigned to oseltamivir was withdrawn due to an SAE of acute onset of angioedema. Serial ECGs and clinical laboratory test results did not reveal any pattern of adverse findings associated with peramivir in comparison with oseltamivir treatment. One death (included in the SAEs) occurred during the treatment period in a subject who did not have confirmed influenza. This subject was assigned to treatment with peramivir 400 mg and received 2 doses prior to the event. The death was attributed to viral myocarditis based on post-mortem histological findings and not considered to be related to study medication by the investigator.

Study BCX1812-301
A Phase 3, Multicenter, Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of Peramivir Administered Intravenously in Addition to Standard of Care Compared to Standard of Care Alone in Adults and Adolescents Who Are Hospitalized Due to Serious Influenza

This was a Phase 3 multinational, randomized, double-blinded trial comparing peramivir to placebo, both administered IV QD for 5 days in addition to the institution's standard of

care (SOC), in adults, adolescents and children ≥ 6 years old who were hospitalized with acute influenza. Subjects were stratified according to duration of illness, standard of care received (NAI-containing antiviral therapy, non-NAI-containing antiviral therapy or no antiviral therapy), laboratory diagnosis of influenza at entry, and whether the subject was admitted to the intensive care unit (ICU) at the time of randomization. Enrollment was to continue until 160 subjects with confirmed influenza who had not received an NAI as part of their SOC regimen (the "Non-NAI SOC subgroup") were enrolled. Eligible subjects were randomized 2:1 to 600 mg peramivir IV QD (adult dosage and maximum dosage for pediatric subjects) or placebo. Subjects who had not met the protocol-defined criteria of clinical resolution on Day 5 or who had detectable virus by RT-PCR from a sample collected on Day 4 after dosing (where available) continued their assigned treatment for another 5 days. Concomitant use of oseltamivir, zanamivir, amantadine, rimantadine, and/or ribavirin was permitted during administration of study drug and in the post-treatment follow-up period where this was in accordance with the institution's SOC.

Efficacy was evaluated through assessments of body temperature, oxygen saturation, vital signs, influenza virus titers, clinical symptoms of influenza, usual daily activities, time to hospital discharge, incidence of influenza-related complications, incidence and duration of ICU admission after initiation of treatment, requirement for continued antiviral treatment beyond Day 5, 30-day mortality following treatment, and changes in viral sensitivity to other antiviral drugs. The primary efficacy endpoint was the same unvalidated clinical endpoint used in Study BCX1812-201; i.e., time to clinical resolution. It was mandatory that both temperature and oxygen saturation meet resolution criteria in order for the clinical resolution endpoint to be met. A hazard ratio (HR) of 0.57 was expected between the two treatment groups based on the time to clinical resolution observed in Study BCX1812-201 and the higher dose of IV peramivir employed in this trial.

A total of 405 subjects were randomized across 86 sites in 20 countries in North America (United States and Canada), South America, Europe, Africa (South Africa), and Asia (India). The trial was conducted from November 2009 to November 2012.

For the primary efficacy endpoint, no significant differences were observed in time to clinical resolution between the two treatment groups for the intent-to-treat infected (ITTI)-Non-NAI population (peramivir 61 subjects, placebo 34 subjects); similar results were noted in the ITTI population. In addition, no significant differences were seen for the secondary or tertiary endpoints for either the ITTI-Non-NAI population or the ITTI population. The overall time to clinical resolution was strongly correlated with time to resolution of fever. Among subjects admitted to the ICU at baseline, a trend was noted toward shorter time to clinical resolution for peramivir-treated subjects (median time 31.5 hours for peramivir [N = 15] versus 50.2 hours for placebo [N = 8]). In a post-hoc multiple regression statistical model, the following baseline characteristics were identified as significant predictors of time to clinical resolution: region (Eastern Europe

versus India; US/Canada versus India), duration of illness, gender, oxygen saturation < 94%, and history of congestive heart failure or angina.

Among subjects with positive viral titers at baseline (as measured by RT-PCR), mean and median viral titers declined rapidly from baseline through 60 hours post-dose and declined more slowly through Day 5. The differences between the two treatment groups, however, were not statistically significant within the ITTI-Non-NAI population

One of the secondary objectives of this trial was to describe the PK of peramivir in hospitalized influenza subjects. The PK findings were generally consistent with prior studies of peramivir, with a geometric mean AUC_{last} of 83,729 ng•hr/mL, a geometric mean C_{max} of 30,798 ng/mL and a geometric mean $T_{1/2}$ of 18.5 hours.

Intravenous peramivir at 600 mg QD was generally safe and well tolerated in this trial. Adverse events were consistent with those expected in a hospitalized influenza population. Overall, the incidence of AEs, ADRs, SAEs, and deaths was similar between the placebo and peramivir treatment groups. Table 4 provides a high-level overview of the major safety results observed in this trial, by treatment group and presence of NAI in the background SOC.

Table 4: Overview of Major Safety Results (Safety Population) - Study BCX1812-301

	Placebo + SOC, n (%)			Peramivir + SOC, n (%)		
	Non-NAI-Containing SOC N = 48	NAI-Containing SOC N = 86	Overall N = 134	Non-NAI-Containing SOC N = 88	NAI-Containing SOC N = 176	Overall N = 264
Any AE	18 (38%)	46 (53%)	64 (48%)	24 (27%)	84 (48%)	108 (41%)
Drug-related AEs[a]	3 (6%)	11 (13%)	14 (10%)	6 (7%)	25 (14%)	31 (12%)
Serious AEs	3 (6%)	10 (12%)	13 (10%)	1 (1%)	14 (8%)	15 (6%)
Deaths	1 (2%)	2 (2%)	3 (2%)	0	1 (1%)	1 (< 1%)
AEs Leading to Study Discontinuation	0	0	0	0	2 (1%)	2 (1%)

AE = adverse event; NAI = neuraminidase inhibitor; SOC = standard of care.
[a] Drug-related AEs were treatment-emergent AEs judged by the Investigator to be possibly, probably, or definitely related to study medication.

Source: Clinical Study Report BCX1812-301

Four subjects died in this trial: 3 who received placebo and 1 who received peramivir. Causes of death were non-overlapping and appeared to be typical of serious complications of influenza (e.g., respiratory arrest, multiorgan disorder, pneumonia, septic shock, staphylococcal infection). Serious AEs were also consistent with serious complications of influenza and no single Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) was reported as an SAE by more than two subjects in

either treatment group. Very few subjects discontinued study due to AEs. No single MedDRA PT was reported by more than 5% of subjects who received peramivir. The most frequently reported AEs among peramivir-treated subjects in this trial were diarrhea (5% peramivir, 7% placebo), nausea (4% peramivir, 7% placebo), and insomnia (4% peramivir, 1% placebo). There did not appear to be important differences in the proportion of AEs reported between the two treatment groups on the basis of MedDRA System Organ Class (SOC). The incidence of laboratory toxicities was also similar between the two groups.

Medical Officer's Comment:
The efficacy of peramivir in hospitalized patients with influenza has not been demonstrated. Given the heterogeneous subject populations in Studies BCX1812-201 and -301 and the high incidence of secondary influenza complications observed in these trials, it is possible that the endpoints selected were not sufficiently sensitive to adequately measure efficacy in this patient population.

Study BCX1812-303
A Phase 3, Open-Label, Randomized Study of the Antiviral Activity, Safety, and Tolerability of Intravenous Peramivir in Hospitalized Subjects with Confirmed or Suspected Influenza Infection

This was a Phase 3 multinational, randomized, open-label trial to evaluate the antiviral activity, safety, and tolerability of IV peramivir (300 mg BID or 600 mg QD) for 5 days in adults and children (≥ 6 years of age) hospitalized with confirmed or suspected influenza infection who did not have clinical or laboratory evidence of severe organ dysfunction. The primary efficacy endpoint was change in influenza virus titer measured by $\log_{10}$ $TCID_{50}$. This endpoint was an objective measure not dependent on subjective evaluation by either study staff or subjects; therefore, an open-label design was considered acceptable to evaluate the endpoint.

Clinical endpoints, procedures, and methods of assessment were similar to those noted for Studies BCX1812-201 and -301. In fact, Study BCX1812-301 was initiated at approximately the same time as this trial and was still ongoing when this trial was completed. However, BCX1812-303 was conducted during the 2009 H1N1 influenza A pandemic. One of the reasons for initiating this trial was to provide access to IV peramivir to seriously ill patients hospitalized with this novel influenza strain. For this reason, the eligibility criteria were intentionally broader with fewer restrictions compared to the other hospitalized trials of peramivir. Importantly, duration of illness, duration of hospitalization, and type and duration of prior antiviral therapy, including NAI use, were not exclusionary criteria for participation in this trial.

Subjects were enrolled at 59 sites in the United States, Canada, Mexico, Australia, and New Zealand from October 2009 to October 2010. Enrollment continued until 234

subjects were enrolled, at which time the Sponsor decided to end enrollment. In the intent-to-treat (ITT) population, the vast majority of subjects were adults (97% in the 300 mg BID group, and 99% in the 600 mg QD group) with ages ranging from 18 to ≥ 75 years. The remaining subjects (N=4) were adolescents (12-17 years); no children under 11 years of age were enrolled. More women (59%) than men were enrolled.

A total of 128 subjects (54%) had confirmed influenza infection, most of whom had the influenza A/H1N1pdm09 subtype (74%, 95/128). The proportion of subjects with this subtype in each treatment group was similar (76% in the 300 mg BID group and 73% in the 600 mg QD group). However, there were other imbalances between the two groups in the ITTI population. For example, the 600 mg QD group had a higher proportion of subjects in the ICU at baseline than the 300 mg BID group (21% versus 16%, respectively); a higher proportion of subjects requiring supplemental oxygen at Screening (74% versus 61%, respectively); and a higher proportion of subjects using corticosteroids at enrollment (59% versus 44%, respectively). In addition, more men and Hispanics were enrolled in the 600 mg QD group. In the ITTI population (N=127), 40% (28/70) of subjects in the 600 mg QD group and 28% (16/57) of subjects in the 300 mg BID group received more than 5 days of peramivir treatment.

In 44 subjects with both a positive baseline and post-baseline viral titer assessments, the overall mean and median time-weighted changes from Baseline in $\log_{10}$ $TCID_{50}$ at 48 hours were identical (-1.51) in the 300 mg BID and 600 mg QD treatment groups, with no differences between the mean and median values. By 48 hours after the beginning of peramivir treatment, 86% of all subjects with positive baseline titers in the ITTI population had a negative virus titer (80% in the 300 mg BID group and 91% in the 600 mg QD group); by 96 hours, all subjects in both treatment groups had negative virus titers. Similar results were seen when viral titers were measured by RT-PCR.

Overall, 65% of subjects (72% in the 300 mg BID group and 60% in the 600 mg QD group) achieved clinical resolution. The overall median time to clinical resolution was 92 hours (45 hours in the 300 mg BID group, 166 hours in the 600 mg QD group). This difference between the two treatment groups was unexpected based on the primary virologic endpoint results. Pre-specified subgroup analyses showed that the time to clinical resolution was longer among subjects whose duration of illness was > 48 hours, who were treated in the Northern Hemisphere, and who were admitted to the ICU at baseline. There appeared to be no differences in time to clinical resolution by gender or viral subtype. Post-hoc analyses using a multiple regression model found that the need for supplemental oxygen use at Screening, admission to the ICU at baseline, and duration of hospitalization prior to study treatment were significant predictors of time to clinical resolution. Subjects who received supplemental oxygen at Screening had a markedly longer median time to clinical resolution (177 hours) compared to subjects who did not (27 hours). There were no important differences in time to clinical resolution between the two peramivir groups when the data were adjusted for need for supplemental oxygen use at Screening.

Ten percent of all subjects in the safety population (N=230) died. Nearly half of all deaths were related to respiratory failure. More subjects in the 600 mg QD group died compared with the 300 mg BID group (12% versus 7%, respectively). Post-hoc analyses of the ITTI population showed that subjects who required supplemental oxygen at baseline had a higher mortality risk compared with those who did not (14% versus 0%, respectively, p = 0.014), and subjects admitted to the ICU at baseline had a mortality risk of 21% compared with 7% for those who were not (p = 0.034). There were no statistical differences between the two treatment groups in 28-day mortality when the need for supplemental oxygen at Screening and ICU admission at baseline were controlled.

Sparse PK sampling parameters in this trial were consistent with those of previous peramivir studies and demonstrated peramivir exposures predictive of efficacy against influenza A/H1N1pdm09 in both treatment regimens.

In this seriously ill hospitalized population, peramivir either at 600 mg QD or 300 mg BID was generally safe and well-tolerated. No clinically relevant differences in safety were noted between the two dosing regimens; however, subjects in the 600 mg QD group were generally sicker. More subjects in the 600 mg QD group reported potentially life-threatening AEs compared with the 300 mg BID group, (19% versus 11%, respectively). Also, 11% of subjects in the 600 mg QD group reported anemia and 6% reported acute renal failure compared with 4% and 1%, respectively, in the 300 mg BID group.

6 Review of Efficacy

Efficacy Summary

The efficacy claim of IV peramivir for the treatment of acute uncomplicated influenza in adults is based primarily on clinical trial data from the Phase 2 Study 0722T0621, an adequate and well-controlled multicenter trial conducted in Japan in nearly 300 subjects during a single influenza season. In this trial, a single dose of IV peramivir, dosed at either 300 mg or 600 mg, shortened the time to alleviation of influenza symptoms by approximately 1 day compared with placebo, a statistically significant and persuasive difference. A caveat to these findings is the fact that subjects in this trial were all Asian, mostly young (median age 32 years), and predominantly infected with influenza A (mostly H1N1). In fact, only three subjects in this trial had influenza B infection. Subjects in this trial also tended to present early for treatment (within 24 hours of influenza symptom onset) and with relatively less severe disease (based on a composite score of initial influenza symptoms). Nonetheless, the peramivir treatment effect was observed across various subgroups and clinical sites in this trial and was consistent across multiple secondary endpoints, such as time to resolution of fever, time to resumption of usual activities, decrease in viral titers from baseline, and decrease in viral shedding. These findings were not affected by acetaminophen use, which was lower in the peramivir groups than in the placebo group.

Supportive efficacy data were derived from the three BioCryst-sponsored clinical trials of IM peramivir, which were conducted in a more diverse global population. Two Phase 1 trials established the bioequivalence of the IM and IV formulations of peramivir so that clinical data from the IM trials could be used in support of IV approval. However, for various reasons, none of the IM peramivir trials matched the results of Study 0722T0621. Nonetheless, in each trial, a numerical improvement in primary and secondary endpoint estimates was seen with peramivir 300 mg or 600 mg compared with placebo. While a 150 mg IM dose of peramivir was also evaluated in one of these trials, this dose was not shown to be as effective as the higher doses. Indeed, a dose-ordered response was noted for the time to alleviation of symptoms in an integrated analysis of the four available placebo-controlled trials. Results of this integrated analysis also corroborated the findings of Study 0722T0621.

In the integrated analysis, there was an overall consistent treatment benefit of peramivir with respect to resolution of influenza symptoms across subgroups based on region, age, gender, race, smoking status, influenza A virus subtype, symptom duration at baseline, and severity of illness. With that being said, some of the subgroups were very small and did not allow for meaningful conclusions to be drawn. Thus, efficacy of peramivir could not be demonstrated in Blacks, Hispanics, the elderly, subjects with symptom duration greater than 36 hours, or subjects infected with influenza B virus. Not

unexpectedly, the efficacy of peramivir was not demonstrated in subjects infected with influenza A/H1N1 with the H275Y substitution.

Resistance-associated substitutions were noted in approximately 1.6% of peramivir-treated subjects across the four placebo-controlled trials. The only influenza A/H1N1 amino acid substitution that developed in more than one subject was the NA H275Y substitution, detected in 7 subjects on peramivir treatment. Among peramivir-treated subjects with influenza A/H3N2 virus, no amino acid substitutions developed in more than one subject. The R292K substitution, conferring resistance to oseltamivir and zanamivir, developed in one peramivir-treated subject. Although not specifically evaluated, there was no documented transmission of resistant virus among subjects who developed treatment-emergent resistance.

In Study 0722T0621 and in the integrated analyses, no notable differences were observed between the 300 mg and 600 mg peramivir doses in terms of efficacy. Selection of the 600 mg dose was based on observation of a dose response in time to alleviation of symptoms in the integrated analysis and in virologic outcomes in Study 0722T0621, and results of PK/PD modeling which suggested that the 600 mg dose would result in more patients exceeding the IC_{50} for a targeted duration in a typical influenza season as well as in a season characterized by low NAI-susceptibility. In the absence of any safety concerns related to the higher dose, the review team concurred with selection of the 600 mg IV peramivir dose for the proposed indication.

6.1 Indication

The proposed indication is treatment of acute uncomplicated influenza in patients 18 years and older.

6.1.1 Methods

The analyses of efficacy were based on the ITTI populations of the respective trials. The ITTI population included all subjects who were enrolled and randomized, received at least one dose of study drug, and had a laboratory diagnosis of influenza. For Studies BCX1812-211 and 0722T0621, this confirmation was based on at least 1 of the following: a positive PCR specimen, a positive viral culture, or paired acute and convalescent serology demonstrating at least a 4-fold increase in antibody titer against influenza A or B. For Studies BCX1812-212 and -311, confirmation of influenza infection was based on a positive PCR specimen or a positive viral culture. Subjects in whom influenza symptoms did not resolve were censored.

Influenza type was determined from PCR and/or serology results where available. Subjects in trials where confirmation of influenza was by RAT only had indeterminate influenza type. Severity of illness was based on the sum of the 7 influenza symptoms from the first complete diary card.

For the review of efficacy, analyses of the pivotal trial (Study 0722T0621) are presented first, followed by analyses of the supportive studies with IM peramivir, followed in turn by integrated analyses of the four placebo-controlled trials.

Because Study BCX1812-311 had a relatively small sample size and it and Study BCX1812-211 employed nearly identical eligibility criteria and study procedures, were conducted in successive influenza seasons, and evaluated the same dose of IM peramivir (300 mg), these two trials were pooled together in the evaluation of efficacy (and safety).

6.1.2 Demographics

Study 0722T0621

Baseline subject demographics and disease characteristics in Study 0722T0621 are presented in Table 5. All randomized and treated subjects in this trial (N=298) were Asian (Japanese). Mean age was 34 years and all subjects were < 65 years of age (as per the protocol). Overall, the ratio of men to women was evenly distributed, although there were more men than women in the peramivir 600 mg IV arm (56% versus 44%, respectively) and more women than men in the peramivir 300 mg IV arm (54% versus 47%, respectively). Otherwise, treatment groups were well balanced with respect to baseline demographic characteristics. Overall mean body mass index (BMI) was 22.8. About a third of all subjects were smokers, and 25% had received influenza vaccination in the previous 12 months.

All subjects in this trial were treated during the 2007-2008 Northern Hemisphere season. Nearly all subjects (99.7%) were confirmed to have influenza infection by PCR; 97% also had positive viral titers on screening cultures. The majority (72%) of subjects were infected with influenza A/H1N1, about a quarter with influenza A/H3N2, and only three subjects were infected with influenza B. Baseline serology data were available for 290 subjects; of these, 11 subjects had baseline antibody titers ≥ 1:16 for influenza A and 3 subjects had baseline antibody titers ≥ 1:16 for influenza B, with comparable numbers in each treatment group. When paired samples from baseline and Day 14 were compared, 129 subjects demonstrated a ≥ 4-fold increase in serum antibodies titers (128 subjects with influenza A and 1 subject with influenza B). The proportion of subjects with ≥ 4-fold antibody response was greater in the placebo group (53%) than in either peramivir group (40-41%).

Duration of illness at the time of screening was between 12 and 36 hours for most subjects, with 54% of subjects presenting within 24 hours. Overall, the mean baseline influenza symptom score was 11.8, with similar scores across the three treatment groups. Most subjects (77%) had composite scores less than 14 at presentation.

Table 5: Baseline Demographic and Disease Characteristics (Treated Subjects) - Study 0722T0621

Baseline Characteristics	Peramivir 300 IV	Peramivir 600 IV	Placebo	Overall
	N=99	N=99	N=100	N=298
Age, years				
Mean (SD)	34.8 (9.8)	34.7 (10.6)	34.8 (9.7)	34.8 (10)
Median	32	32	32	32
Min, Max	20, 60	20, 62	21, 62	20, 62
Sex, n (%)				
Female	53 (54)	44 (44)	49 (49)	146 (49)
Male	46 (47)	55 (56)	51 (51)	152 (51)
Race, n (%)				
Asian	99 (100)	99 (100)	100 (100)	298 (100)
Body Mass Index (kg/m^2)				
Mean (SD)	22.8 (4.2)	23.1 (4.1)	22.5 (3.8)	22.8 (4.0)
Median	22	23	22	22
Min, Max	16, 45	17, 37	26, 35	16, 45
Smoker, n (%)				
No	65 (66)	65 (66)	66 (66)	196 (66)
Yes	34 (34)	34 (34)	34 (34)	102 (34)
Vaccination in last 12 months, n (%)				
No	76 (77)	72 (73)	76 (76)	224 (75)
Yes	23 (23)	27 (27)	24 (24)	74 (25)
Initial Composite Score				
Mean (SD)	11.5 (2.8)	11.8 (2.5)	12 (2.7)	11.8 (2.6)
Median	11	11	12	11
Min, Max	6, 20	6, 19	6, 21	6, 21
< 14, n (%)	80 (81)	76 (77)	74 (74)	230 (77)
≥ 14, n (%)	19 (19)	23 (23)	26 (26)	68 (23)
Duration of Illness, n (%)				
0 to 12 hours	17 (17)	10 (10)	8 (8)	35 (12)
12 to 24 hours	42 (42)	43 (43)	40 (40)	125 (42)
24 to 36 hours	22 (22)	31 (32)	30 (30)	83 (28)
36 to 48 hours	18 (18)	15 (15)	22 (22)	55 (19)
Confirmed Influenza, n (%)				
Infected	99 (100)	98 (99)	100 (100)	297 (100)
PCR	99 (100)	98 (99)	100 (100)	297 (100)
Viral titer [a]	96 (97)	95 (96)	97 (97)	288 (97)
Serology, n/N (%) [b]	38/96 (40)	40/97 (41)	51/97 (53)	129/290 (45)
Not Infected	0	1 (1)	0	1 (<1)
Influenza Subtype, n (%)				
A/H1N1	74 (75)	70 (71)	72 (72)	216 (72)

A/H3N2	21 (21)	25 (25)	24 (24)	70 (23)
A/Indeterminate	2 (2)	2 (2)	4 (4)	8 (3)
B	2 (2)	1 (1)	0	3 (1)

a) Positive viral titer was defined as > 1.2 log10(TCID50/mL)
b) N = number of subjects with baseline serology; n = number of subjects with ≥ 4-fold increase in antibody titer from screening to Day 14 assessment.

Source: created by clinical reviewer using analysis subject level dataset (ADSL xpt) and laboratory dataset (LB.xpt) – Study 0722T0621

Studies BCX1812-211, -311, and -212

Baseline subject demographics and disease characteristics for the three BioCryst trials of IM peramivir are presented in Table 6. Baseline characteristics for Studies BCX1812-211 and -311are pooled together and presented alongside those of BXC1812-212.

The study populations in the IM peramivir trials were similar to each other but showed differences compared to the pivotal trial, Study 0722T0621, conducted in Japan. Due to inclusion/exclusion criteria, subjects in Study 0722T0621 had a more limited age range compared to subjects in the BioCryst trials; however, mean and median ages were similar across trials and across treatment groups. That said, despite the broader age criteria, few elderly subjects (≥ 65 years) were enrolled in the BioCryst trials (approximately 2% overall). The BioCryst trials were relatively well balanced by gender, although there were some variations within the treatment groups. In particular, the 150 mg IM peramivir treatment group enrolled a higher percentage of women (59%) than the other treatment groups (49% to 52%). Very few subjects in the BioCryst trials were enrolled in Asia; most were treated in North America or other parts of the world. Consequently, subjects in these trials were predominantly White or Caucasian, with a much smaller percentage of Black or African-American subjects, Asian subjects, or subjects of other races. Over 90% of treated subjects were Non-Hispanic (or were of unknown ethnicity, as BCX1812-212 did not collect ethnicity data). The IM peramivir treatment groups were relatively well balanced by height, weight, BMI, and smoking status. In general, these subjects were taller, weighed more, had higher BMIs, and were less likely to be current smokers than the Japanese subjects of Study 0722T0621. Vaccination status information was not collected in the BioCryst trials.

In contrast to Study 0722T0621, which took place entirely during the 2007-2008 Northern Hemisphere season, the BioCryst IM peramivir trials were conducted across multiple influenza seasons. Study BCX1812-211/311 enrolled subjects during the 2006-2007 Northern Hemisphere, 2007 Southern Hemisphere, and 2007-2008 Northern Hemisphere seasons; and Study BCX1812-212 enrolled subjects during the 2008 Southern Hemisphere season and the 2008-2009 Northern Hemisphere season. Influenza subtype varied by trial as a result of seasonal variation in circulating influenza strains. Notably, in Study BCX1812-212 approximately 57% of treated subjects had infection with the H275Y variant of influenza A/H1N1; this variant was not represented in the other placebo-controlled trials. Study BCX1812-211/311 included the widest

variety of influenza subtypes: approximately half (49%) of treated subjects had influenza A/H3N2; one-fourth had wild type influenza A/H1N1; and 18% had influenza B.

For the majority of subjects enrolled in the BioCryst trials, influenza infection was confirmed via PCR and/or viral culture. Serology information was not collected in Studies BCX1812-212 or -311. In Study BCX1812-211, baseline serology data were only available in 27 subjects (8% of the enrolled study population); of these, only four subjects had a 4-fold increase in antibody titers by paired (acute and convalescent) serology: two subjects with influenza A (1 each for A/H1N1 and A/H3N2) and two subjects with influenza B. None of these four subjects had a positive PCR, but 3 of the 4 had positive titers on viral culture. Thus, only one subject (with influenza A/H1N1, and treated with peramivir 300 mg IM) had influenza confirmed based solely on serology.

In contrast to Study 0722T0621, where a higher percentage of subjects were enrolled within 12 or 24 hours of onset of symptoms, most subjects in the BioCryst trials were enrolled beyond 24 hours of illness duration. Subjects with illness duration > 36 hours were excluded from Study BCX1812-212; therefore, duration of illness was shorter in this trial, but severity of illness was similar to that seen in BCX1812-211/311. Severity of illness was also higher in the BioCryst trials overall compared to Study 0722T0621 (mean initial composite score > 14 versus 11.8, respectively).

Table 6: Baseline Demographic and Disease Characteristics (Treated Subjects) – Studies BCX1812-211 and -311 (Pooled) and BCX1812-212

Baseline Characteristics	BCX1812-211/311			BCX1812-212	
	Peramivir 150 IM	Peramivir 300 IM	Placebo	Peramivir 600 IM	Placebo
	N=113	N=172	N=139	N=200	N=202
Age, years					
Mean (SD)	36.8 (15.5)	35.5 (13.1)	34.4 (11.5)	35 (12.1)	35.2 (11.3)
Median	32	32	32	32	34
Min, Max	17, 92	18, 84	18, 64	18, 81	18, 71
Age Group, n (%)					
≥12 to < 18 years	1 (1)	0	0	0	0
≥18 to < 65 years	104 (92)	168 (98)	139 (100)	196 (98)	200 (99)
≥ 65 to < 75 years	5 (4)	2 (1)	0	3 (2)	2 (1)
≥ 75 years	3 (3)	2 (1)	0	1 (<1)	0
Sex, n (%)					
Female	67 (59)	90 (52)	68 (49)	100 (50)	104 (52)
Male	46 (41)	82 (48)	71 (51)	100 (50)	98 (48)
Race, n (%)					
White	78 (69)	122 (71)	92 (66)	105 (53)	100 (50)

Black/African American	18 (16)	21 (12)	23 (17)	61 (31)	68 (34)
Asian	4 (4)	9 (5)	9 (7)	15 (8)	15 (7)
Native Hawaiian/Other Pacific Islander	8 (7)	5 (3)	6 (4)	3 (2)	5 (3)
Other	5 (4)	15 (9)	9 (6)	16 (8)	14 (7)
Ethnicity, n (%)					
Hispanic Or Latino	9 (8)	13 (8)	12 (9)	0	0
Not Hispanic Or Latino	104 (92)	111 (65)	108 (78)	0	0
Unknown	0	48 (28)	19 (14)	200 (100)	202 (100)
Region, n (%)					
North America	44 (39)	104 (60)	69 (50)	88 (44)	88 (44)
Asia	1 (1)	1 (1)	3 (2)	0	0
ROW	68 (60)	67 (39)	67 (48)	112 (56)	114 (56)
BMI (kg/m^2)					
Mean (SD)	27.4 (6.2)	27.9 (6.3)	26.6 (6.0)	27.3 (6.3)	27.5 (6.8)
Median	26	26	25	26	25
Min, Max	17, 50	17, 49	16, 49	16, 50	17, 51
Smoker, n (%)					
No	91 (81)	133 (77)	109 (78)	164 (82)	165 (82)
Yes	22 (19)	39 (23)	30 (22)	36 (18)	37 (18)
Initial Composite Score					
N	113	171	137	197	198
Mean (SD)	14.4 (3.2)	14.5 (3.7)	14.3 (3.9)	14.4 (3.9)	14.4 (4.3)
Median	14	15	14	14	14
Min, Max	7, 21	4, 21	3, 21	3, 21	, 21
< 14, n/N (%)	46 (41)	61 (36)	52 (38)	79 (40)	78 (39)
≥ 14, n/N (%)	67 (59)	110 (64)	85 (62)	118 (60)	120 (61)
Duration of Illness, n (%)					
0 to 12 hours	4 (4)	8 (5)	2 (1)	16 (8)	13 (6)
12 to 24 hours	32 (28)	40 (23)	43 (31)	80 (40)	91 (45)
24 to 36 hours	43 (38)	66 (38)	53 (38)	104 (52)	98 (49)
36 to 48 hours	34 (30)	58 (34)	41 (30)	0	0
Influenza Season, n (%)					
Northern Hemisphere 2006-2007	44 (39)	47 (27)	46 (33)	0	0
Southern Hemisphere 2007	68 (60)	67 (39)	65 (47)	0	0
Northern Hemisphere 2007-2008	1 (1)	58 (34)	28 (20)	0	0
Southern Hemisphere 2008	0	0	0	112 (56)	114 (56)
Northern Hemisphere 2008-2009	0	0	0	88 (44)	88 (44)
Confirmed Influenza, n (%)					
Infected	104 (92)	163 (95)	134 (96)	160 (80)	174 (86)

PCR	100 (89)	150 (87)	128 (92)	160 (80)	174 (86)
Viral titer [a]	96 (85)	154 (90)	127 (91)	122 (61)	147 (73)
Serology, n/N (%) [b]	0/9 (0)	3/12 (25)	1/6 (17)	--	--
Not infected	9 (8)	9 (5)	5 (4)	40 (20)	28 (14)
Influenza Subtype, n (%)					
A/H1N1	32 (28)	37 (21)	35 (25)	11 (6)	4 (2)
A/H1N1 H275Y	0	0	0	105 (53)	125 (62)
A/H3N2	50 (44)	90 (52)	68 (49)	16 (8)	20 (10)
A/Indeterminate	3 (3)	2 (1)	3 (2)	1 (1)	0
A+B	0	2 (1)	1 (1)	0	0
B	19 (17)	29 (17)	27 (19)	27 (14)	25 (13)
Indeterminate	0	3 (2)	0	0	0

Abbreviations: ROW = Rest of the World (Australia, Great Britain, New Zealand, South Africa)
a) Positive viral titer was defined as > 0.5 log10(TCID50/mL)
b) N = number of subjects with baseline serology; n = number of subjects with ≥ 4-fold increase in antibody titer from screening to Day 14 assessment.
Source: created by clinical reviewer using analysis subject level datasets (ADSL.xpt) – Studies BCX1812-211/311 (Integrated) and BCX1812-212, and laboratory dataset (LB.xpt) - Study BCX1812-211

In summary, although there were differences between the trials with respect to baseline demographics, the overall subject population evaluated in these four-placebo controlled trials was consistent with the proposed target population; i.e. adults with acute uncomplicated influenza. Then again, subjects with influenza B, elderly subjects (≥ 65 years), Hispanic subjects, and Black or African-American subjects were underrepresented. Population PK studies, however, have not indicated any significant differences in peramivir exposure based on baseline covariates.

6.1.3 Subject Disposition

Study 0722T0621

Table 7 shows the subject disposition in Study 0722T0621. A total of 300 subjects enrolled in this trial. Shionogi did not report the number of individuals evaluated for enrollment or the number of screen failures. Two randomized subjects, one in the peramivir (PRV) 600 mg IV group (Subject 061-1) and one in the placebo group (Subject 180-5), were never treated as they were determined post-randomization not to have met eligibility criteria.

A total of 298 subjects were treated with study drug: 99 in each peramivir arm and 100 in the placebo group; for the FDA analyses, these subjects constituted the safety population. The vast majority of treated subjects in this trial were confirmed by PCR to be infected with influenza (N=297) and made up the ITTI population used in the primary efficacy analyses.

Of the 298 treated subjects, 291 (98%) completed the trial and seven (2%) discontinued prematurely. The reasons for discontinuation are listed in Table 7. One subject treated with peramivir 600 mg (Subject 077-6) was later found to have had a violation of exclusion criteria (complications of bronchial asthma requiring drug therapy) and was discontinued from the study on the morning of Day 3. This subject was infected with influenza A/H1N1, but no further assessments were collected beyond Day 3. Another subject in the placebo group (Subject 187-4) was discontinued on Day 8 due to worsening of cough, which was cited as an AE. Given the small numbers, no significant differences could be discerned among the three treatment arms regarding reasons for study discontinuation. Of the three subjects who withdrew consent, only one (Subject 154-3 in the PRV 600 mg group, who withdrew on Day 9) had any AEs reported. The AEs (eczema, eosinophil count increased, and monocyte count increased) were mild, occurred within 1-3 days of study drug infusion, and were considered possibly related to study drug by the investigator.

Table 7: Subject Disposition - Study 0722T0621

	Peramivir 300 IV	Peramivir 600 IV	Placebo	Total
Randomized (ITT)	99	100	101	300
Randomized but Not Treated	0	1	1	2
Treated (Safety), N (%)	99 (100)	99 (100)	100 (100)	298 (100)
Treated and Infected (ITTI), n (%)	99 (100)	98 (99)	100 (100)	297 (100)
Completed, n (%)	97 (98)	95 (96)	99 (99)	291 (98)
Discontinued, n (%)	2 (2)	4 (4)	1 (1)	7 (2)
Lost to Follow-up	1 (1)	0	0	1 (<1)
Ineligible	0	1 (1)	0	1 (<1)
Adverse Event	0	0	1 (1)	1 (<1)
Protocol Deviation/Violation	0	1 (1)	0	1 (<1)
Subject Withdrew Consent	1 (1)	2 (2)	0	3 (1)

Source: created by clinical reviewer using analysis subject level dataset (ADSL.xpt) – Study 0722T0621

Studies BCX1812-211 and-311 (Pooled)

A total of 2,115 individuals were screened for enrollment in Study BCX1812-211. Of these, 1,771 were excluded from participation, with a negative RAT being the most common reason. A total of 344 subjects were judged to meet criteria for enrollment and were randomized. However, two subjects (Subject 026001 in the PRV 150 mg group and Subject 673003 in the placebo group) were determined after randomization not to have met the inclusion criteria because of a negative RAT and were withdrawn from the trial before receiving study drug. Of the 342 remaining subjects, 114 received placebo, 113 received PRV 150 mg IM, and 115 received PRV 300 mg IM.

A total of 116 individuals were screened for enrollment in Study BCX1812-311prior to termination of the trial. Of these, 34 were excluded from participation, with a negative RAT being the most common reason. A total of 82 subjects met criteria for enrollment and were randomized: 57 subjects received PRV 300 mg IM and 25 subjects received placebo.

Subject disposition in Studies BCX1812-211 and -311 is presented in Table 8. Of the 426 randomized subjects in the pooled set, 139 received placebo, 113 received PRV 150 mg IM, and 172 received PRV 300 mg IM. These subjects constitute the ITT and safety population used for this review. The ITTI population used for the efficacy analyses included all subjects who were randomized, received at least one injection of study drug, and had proven influenza infection by positive viral titer at any visit, positive PCR, or paired serology (≥ 4-fold increase in HAI antibody to influenza A or B). Influenza infection was confirmed in 134 (96%), 104 (92%), and 163 (95%) subjects who received placebo, PRV 150 mg, and PRV 300 mg, respectively. As noted in Section 6.1.2, influenza was confirmed by PCR and/or viral culture in the majority of ITTI subjects; only 1 subject in the PRV 300 mg group had confirmation based only on serology.

Of the 424 treated subjects, 414 (95%) completed study and 10 (2%) withdrew prematurely. Twice as many subjects withdrew from the PRV 300 mg group than from the placebo group (6 versus 3, respectively). The reasons for discontinuation are listed by treatment arm in Table 8. Most subjects who discontinued prematurely were either lost to follow-up or withdrew consent. Two subjects in Study BCX1812-311 (Subject 643009 in the placebo group and Subject 643001 in the PRV 300 mg group) discontinued early because the sponsor terminated the trial; Subject 643001was given the option to complete the study but opted to withdraw instead. Another subject in the PRV 300 mg group of Study BCX1812-211 (Subject 653022) discontinued on Day (b) (6) because of an SAE (headache and vomiting, subsequently diagnosed as meningitis that led to death); the event was considered unlikely related to study drug by the investigator. This subject was confirmed to be infected with influenza A/H3N2 by PCR.

Table 8: Subject Disposition - Studies BCX1812-211 and -311 (Pooled)

	Peramivir 150 IM	Peramivir 300 IM	Placebo	Total
Screened				2231
Screen Failures				1805
Randomized (ITT)	114	172	140	426
Randomized but Not Treated	1	0	1	2
Treated (Safety), N (%)	113 (100)	172 (100)	139 (100)	424 (100)
Treated and Infected (ITTI), n (%)	104 (92)	163 (95)	134 (96)	401 (95)
Completed, n (%)	112 (99)	166 (97)	136 (98)	414 (98)
Discontinued, n (%)	1 (1)	6 (3)	3 (2)	10 (2)

Lost to Follow-up	1 (1)	2 (1)	2 (1)	5 (1)
Adverse Event	0	1 (1)	0	1 (<1)
Sponsor Terminated Study	0	0	1 (1)	1 (<1)
Subject Withdrew Consent	0	3 (2)	0	3 (1)

Source: created by clinical reviewer using analysis subject level dataset (ADSL xpt) – Studies BCX1812-211/311 (Integrated)

In its analysis of efficacy for the integrated Studies BCX1812-211 and -311, the Applicant excluded two subjects due to missing data; both subjects were treated with placebo. In Study BCX1812-211, there was insufficient data from Subject 673010 to enable determination of efficacy as the subject was lost to follow-up after Day 1 and no self-assessments were available for review; this subject was confirmed to be infected with influenza A/H3N2. In Study BCX1812-311, there was insufficient data from Subject 643009; this subject discontinued study on Day 3 because the sponsor terminated the trial and apparently no self-assessments were collected at all from this subject. This subject was confirmed to be infected with influenza A/H1N1. For the review of efficacy, this reviewer censored these two subjects at 0 hours rather than excluding them from the analyses.

As noted in Section 3.2, one investigator site inadvertently discarded subject records for Studies BCX1812-211 and -311. As a result, 17 subjects treated at that site were excluded from the FDA analyses of efficacy and safety. Sixteen of these 17 subjects were confirmed to have influenza infection. Table 9 presents the revised ITTI and safety population numbers for the pooled Studies BCX1812-211/311 after exclusion of these 17 subjects.

Table 9: Revised Safety and ITTI Populations for Studies BCX1812-211 and -311 (Pooled)

	Peramivir 150 IM	Peramivir 300 IM	Placebo	Total
Excluded from Analyses, n	5	7	5	17
Evaluable Safety, n	108	165	134	407
Evaluable ITTI, n	100	156	129	385

Study BCX1812-212

Subject disposition in Study BCX1812-212 is presented in Table 10. A total of 2,119 individuals were evaluated for enrollment; of these, 1,714 were screen failures, the vast majority of which were due to RAT negative results. A total of 405 individuals met criteria for enrollment and were randomized: 202 to PRV 600 mg IM and 203 to placebo. Three subjects were randomized but not treated (PRV 2, placebo 1); thus, 200 subjects (99%) in the PRV group and 202 subjects (99%) in the placebo group received study drug and constituted the ITT and safety populations. A high percentage of subjects in each group (99%) completed the trial and only three subjects in each group prematurely discontinued the study (all lost to follow-up). On the other hand, influenza

infection was confirmed at a lower rate (83%) in this trial compared to the other placebo-controlled trials of peramivir (~100% in Study 722T0621 and 95% in Studies BCX1812-211/311). The reasons for this are not clear, but are probably related to the sensitivity of the PCR assay used in this trial against influenza strain circulating that season.

Because the IC_{50} of peramivir against influenza B is higher than that for influenza A, the Applicant based the primary efficacy analysis for this trial on the population of treated subjects infected with the more sensitive influenza A viruses (ITTI-A). A total of 282 subjects made up the ITTI-A population, which represented about 70% of all treated subjects. The proportion of treated subjects infected with influenza A virus was higher in the placebo arm than in the peramivir arm (74% versus 67%, respectively).

Medical Officer's Comment:
The Applicant selected the ITTI-A population for the efficacy analyses of Study BCX1812-212 in order to increase the likelihood of demonstrating a treatment effect. For the FDA analyses, the ITTI population was used to maintain consistency of approach across the various placebo-controlled trials. These considerations were not likely to have a significant impact in this case as the majority of influenza A cases in Study BCX1812-212 were H1N1 with the H275Y substitution.

Table 10: Subject Disposition - Study BCX1812-212

	Peramivir 600 IM	Placebo	Total
Screened			2119
Screen Failures			1714
Randomized (ITT)	202	203	405
Randomized but Not Treated	2	1	3
Treated (Safety), N (%)	200 (100)	202 (100)	402 (100)
Treated and Infected (ITTI), n (%)	160 (80)	174 (86)	334 (83)
Infected with influenza A (ITTI-A), n (%)	133 (67)	149 (74)	282 (70)
Completed, n (%)	197 (99)	199 (99)	396 (99)
Discontinued, n (%)	3 (2)	3 (2)	6 (2)
Lost to Follow-up	3 (2)	3 (2)	6 (2)
Evaluable, n (%)	199 (100)	200 (99)	399 (99)

Source: created by clinical reviewer using analysis subject level dataset (ADSL xpt) – Study BCX1812-212

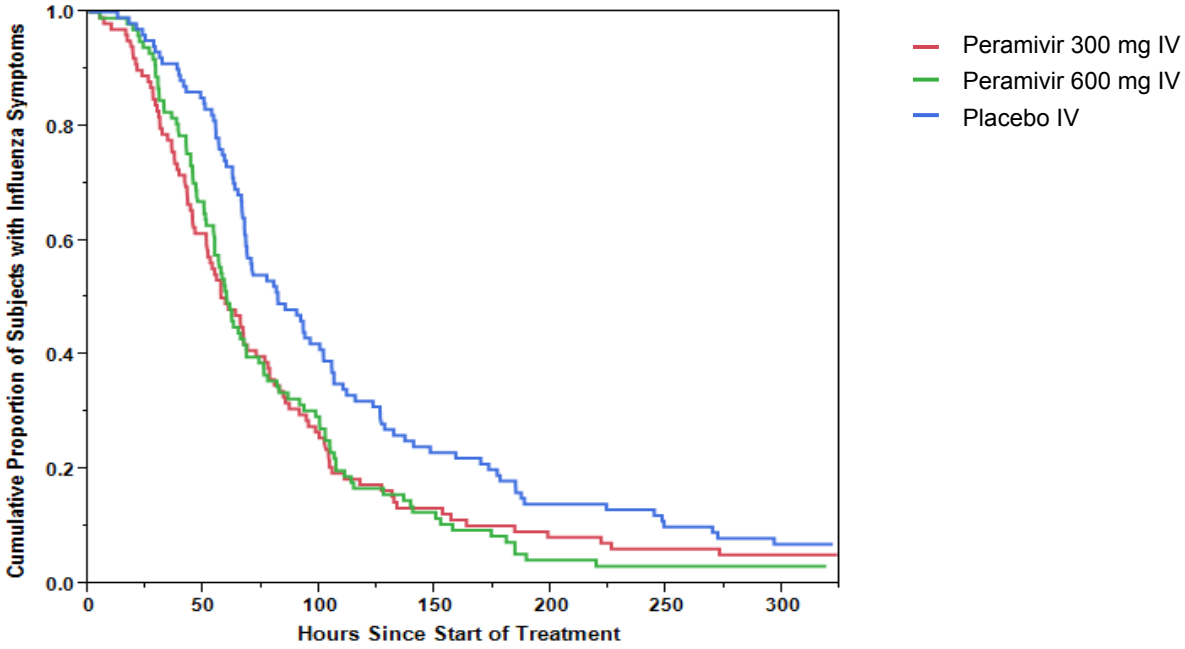
In its analyses of the primary efficacy endpoint, the Applicant excluded three subjects, Subject 311077 in the PRV 600 mg group and Subjects 311152 and 433004 in the placebo group, due to missing diary data.

6.1.4 Analysis of Primary Endpoint(s)

Study 0722T0621

In the pivotal Study 0722T0621, both peramivir 300 mg and 600 mg demonstrated shortening of TTAS compared with placebo. Figure 2 shows the Kaplan-Meier curves for the duration of influenza symptoms in the three treatment groups. The median TTAS was 59.1 hours in the PRV 300 mg IV group, 59.9 hours in the PRV 600 mg IV group, and 81.1 hours in the placebo group. The difference in duration of influenza symptoms in comparison with placebo was -22.7 hours and -21.9 hours for PRV 300 mg and 600 mg, respectively, both of which were statistically significant. When the two peramivir groups were pooled, the difference between peramivir and placebo was also statistically significant with a one-sided *P* value of 0.0010 per the Applicant. Of note, the vast majority of subjects in this trial were infected with influenza A (72% H1N1, 23% H3N2).

Figure 2: Kaplan-Meier Curves for Duration of Influenza Symptoms (ITTI) - Study 0722T0621



Source: created by clinical reviewer using analysis efficacy time to event dataset (ADTTE.xpt) - Study 0722T0621

Acetaminophen use was slightly higher among subjects in the placebo group (77%) than in the peramivir groups (PRV 300 mg 68%, PRV 600 mg 70%); however, the differences were not significant.

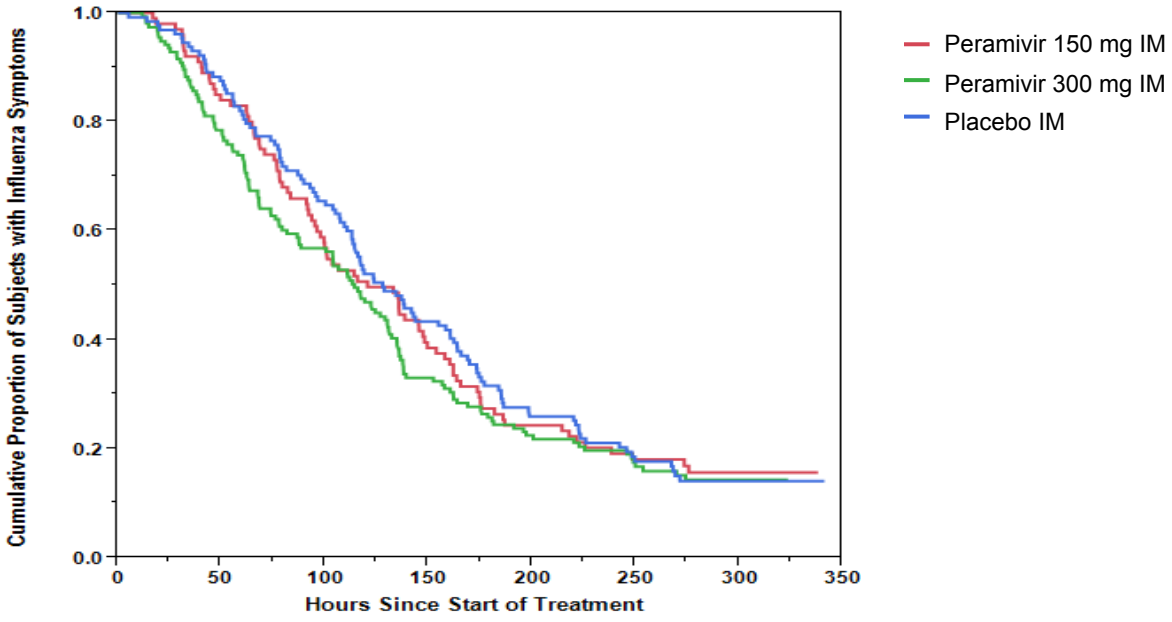
Please refer the Biostatistics review by Dr. Thomas Hammerstrom for further details of the FDA statistical analysis of this pivotal trial.

Studies BCX1812-211 and -311 (Pooled)

Study BXC1812-211 did not meet its primary endpoint; however, the median TTAS for the 150 mg and 300 mg peramivir groups were numerically shorter compared with placebo. Study BCX1812-311 was terminated early, thus no statistical testing was performed on the 79 subjects that made up the ITTI population in that trial.

When efficacy data from these two trials were pooled, the median TTAS for the PRV 150 mg, PRV 300 mg, and placebo groups was 120.7 hours, 114.3 hours, and 127.9 hours, respectively. The differences in the duration of influenza symptoms between the peramivir groups and placebo were not significant, although the PRV 300 mg group demonstrated the shortest time to alleviation. Figure 3 shows the Kaplan-Meier curves for the duration of influenza symptoms by treatment group in this integrated analysis. Please refer to the FDA Biostatistics review for further discussion of this integrated approach to the BioCryst trials.

Figure 3: Kaplan-Meier Curves for Duration of Influenza Symptoms (ITTI) - Studies BCX1812-211/311 (Pooled)



Source: created by clinical reviewer using using analysis efficacy time to event dataset (ADTTE xpt) - Studies BCX1812-211/311 (Integrated)

Study BCX1812-212

Because Study BCX1812-212 was conducted during a season in which the dominant circulating strain of influenza A/H1N1 virus had the NA H275Y substitution, reduced susceptibility to peramivir was noted and no statistically significant differences were observed between PRV 600 mg IM and placebo for the primary endpoint, for either the ITTI-A or ITTI populations. However, subjects who received PRV 600 mg had a numerical improvement compared with subjects who received placebo: median TTAS 91.1 versus 106.9 hours, respectively, in the ITTI-A population and 92.6 versus 107.1 hours, respectively, in the ITTI population. When subjects with the H275Y substitution (N=208) were excluded from the analyses, the resultant sample size was too small to determine an effect of peramivir; median TTAS for non-H275Y subjects was 110.9 hours and 106.3 hours in the PRV 600 mg and placebo groups, respectively. Nevertheless, numerical trends towards shorter TTAS were noted in subjects treated with PRV 600 mg with influenza A (H1N1 wild type and H3N2). No such differences from placebo were noted in subjects with influenza B, although the numbers of evaluable subjects with influenza B were very small (PRV 600 mg N=25, placebo N=23).

Integrated Analysis of Placebo-Controlled Trials

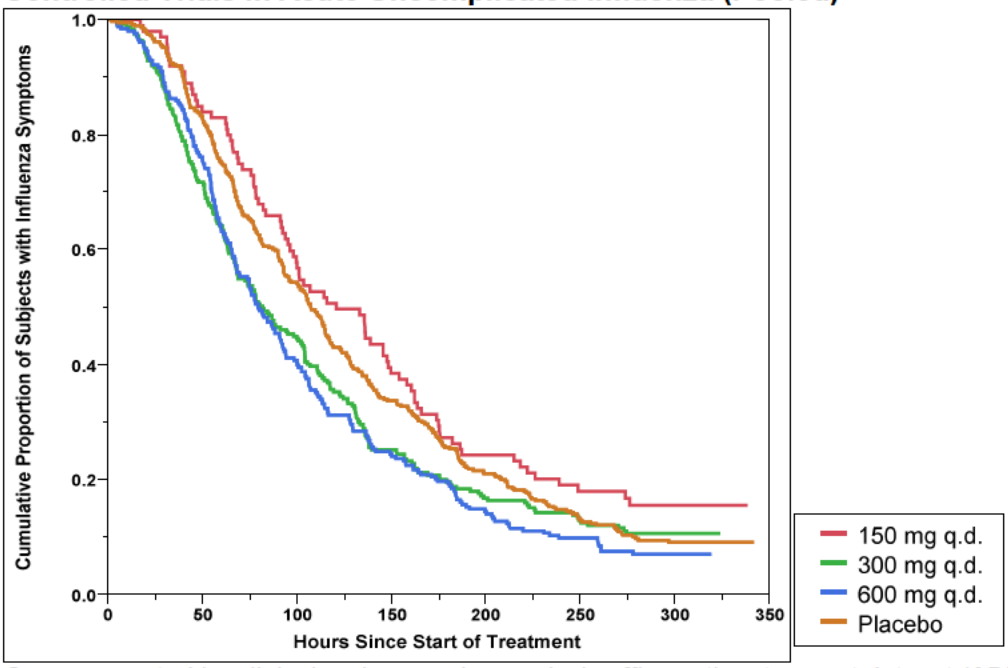
To corroborate the primary endpoint results of Study 0722T0621, as this was the only placebo-controlled trial to convincingly demonstrate a peramivir effect on duration of influenza symptoms, a pooled sensitivity analysis was done combining efficacy data from the four placebo-controlled trials of peramivir in adults with acute uncomplicated influenza (Studies 0722T0621, BCX1812-211, -311, and -212). For this analysis, the Applicant's convention of excluding subjects with missing diary data was adopted. The results of this integrated analysis are displayed in Table 11 and the corresponding Kaplan-Meier curves are in Figure 4.

Table 11: Median Time to Alleviation of Symptoms by Treatment Group (ITTI) - Placebo-Controlled Trials in Acute Uncomplicated Influenza (Pooled)

Kaplan-Meier Estimate	Peramivir 150 mg	Peramivir 300 mg	Peramivir 600 mg	Peramivir Overall	Placebo
N (number censored)	N=100 (17)	N=255 (33)	N=256 (22)	N=611 (72)	N=399 (41)
Median TTAS, hours	120.7	81.7	79.4	87.6	107.3
(95% CI)	(96.1, 148.1)	(68.1, 102)	(68.1, 91.6)	(78.3 - 96.1)	(95.7, 115.2)
25% - 75%	69.8 - 186.8	44 - 152	50.5 - 141.6	50.5 -160.5	60.1 - 184.6

Source: created by clinical reviewer using the analysis efficacy time to event dataset (ADTTE xpt) - Integrated Summary of Efficacy (ISE)

Figure 4: Kaplan-Meier Curves for Duration of Influenza Symptoms (ITTI) - Placebo-Controlled Trials in Acute Uncomplicated Influenza (Pooled)



Source: created by clinical reviewer using analysis efficacy time to event dataset (ADTTE.xpt) - Integrated Summary of Efficacy (ISE)

The overall median TTAS for peramivir-treated subjects in the pooled analysis was 87.6 hours, which represented a substantial improvement compared with placebo (107.4 hours). Similar trends were noted in the individual trials, with subjects treated with peramivir demonstrating a more rapid TTAS compared with subjects who received placebo. As shown in Figure 4, the duration of influenza symptoms was shortest in subjects treated with peramivir 300 mg and 600 mg, with no discernable difference between these two dose groups. The PRV 150 mg dose fared worse than placebo in the integrated analysis and should probably not be relied upon to treat acute influenza. The difference between peramivir and placebo was greater still when the analysis was limited to just the PRV 300 mg and 600 mg doses, where the median TTAS for the pooled peramivir group was 80.3 hours. Taken together, these observations support the primary endpoint findings of Study 0722T0621.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints varied across the four placebo-controlled trials in adults with acute uncomplicated influenza; with Study 0722T0621 having the most (see Table 3). For this review, secondary endpoints that were common to all four trials or considered most clinically relevant were analyzed. These included:

- Time to resolution of fever
- Virologic endpoints
- Time to resumption of usual daily activities

Time to resolution of fever

Fever was one component of the TTAS primary endpoint and also a separate secondary efficacy endpoint in the placebo-controlled clinical trials. However, the analysis of fever data varied across trials. In the BioCryst-sponsored trials, resolution of fever was defined as the time when oral temperature was < 37.2°C (99.0°F) for at least 12 hours without having taken any antipyretic medications for at least 12 hours. In Study 0722T0621, resolution of fever was defined as the time when axillary temperature was < 37.0°C for at least 12 hours and subjects were off antipyretic medications for at least 4 hours.

Table 12 presents the median time to resolution of fever using the BioCryst method for each of the four placebo-controlled trials and the integrated dataset. Across the BioCryst trials, subjects treated with peramivir experienced a shorter time to resolution of fever compared with subjects who received placebo. The differences between peramivir and placebo were greater in Studies BCX1812-211/311 than in BCX1812-212, undoubtedly owing to the predominance of an influenza A/H1N1 strain with decreased susceptibility in the latter trial. In Study 0722T0621, time to resolution of fever by the BioCryst method was much shorter compared with the BioCryst trials, with no discernable difference noted between the treatment groups. However, when the Study 0722T0621 protocol-defined method for calculating the endpoint was used, the median time to resolution of fever (< 37.0°C) was 29.3 hours in the PRV 300 mg group, 30.2 hours in the PRV 600 mg group, and 42.4 hours in the placebo group, with subjects in both the PRV 300mg and 600 mg groups showing substantial reductions in time compared with the placebo group. In the integrated analysis (using the BioCryst method), subjects treated with peramivir had a median time to resolution of fever of 40.8 hours, which per the Applicant was a significant reduction (-6.6 hours) compared to placebo. Please see the Biostatics review by Dr. Thomas Hammerstrom for further analysis of time to resolution of fever in the placebo-controlled trials of peramivir.

Table 12: Median Time to Resolution of Fever by Treatment Group (ITTI) - Placebo-Controlled Trials in Acute Uncomplicated Influenza

Clinical Trial	N = Number of Subjects (censored) Kaplan-Meier Estimate Median Time to Resolution of Fever (hours) (95% CI)				
	Peramivir 150 mg	Peramivir 300 mg	Peramivir 600 mg	Peramivir Total	Placebo
0722T0621		N=99 (1)	N=97 (0)	N=196 (1)	N=100 (0)
		28.4 (21.7 - 31.8)	28.5 (21.5 - 30.8)	28.5 (24.3 - 30.1)	29.4 (24.1 - 34.4)
BCX1812-211/311	N=88 (1)	N=127 (4)		N=215 (5)	N=106 (4)
	53 (43.6 - 63.5)	42.8 (40.3 - 46.1)		44.7 (42.7 - 51)	67.2 (56 - 75.9)
BCX1812-212			N=125 (1)	N=125 (1)	N=131 (3)
			56.8	56.8	60.1

			(44.8 - 77.8)	(44.8 - 77.8)	(49.3 - 65.8)
Integrated	N=88 (1)	N=226 (5)	N=222 (1)	N=536 (7)	N=337 (7)
	53 (43.6 - 63.5)	39.1 (32.3 - 41)	38.4 (31.5 - 43.3)	40.8 (39-43.7)	47.2 (43.3 - 55.6)

Source: created by clinical reviewer using the analysis efficacy time to event dataset (ADTTE xpt) - Integrated Summary of Efficacy (ISE)

Virologic Endpoints

For the analyses of virologic endpoints, data from Studies 0722T0621 and BCX1812-211/311 were evaluated. Data from Study BCX1812-212 were excluded because the predominant circulating strain in that trial was influenza A/H1N1 with the H275Y substitution, which conferred decreased susceptibility to NAIs.

Table 13 shows the change in viral titers, defined as the time-weighted change from baseline in $\log_{10}$ tissue culture infective $dose_{50}$ ($TCID_{50}$/mL), summarized by treatment group and study day for each trial as well as for the integrated analysis. Only the 300 mg and 600 mg doses are shown for peramivir; however, the PRV 150 mg group is counted in the peramivir total results for Study BCX1812-211 and the pooled analysis.

In general, treatment with peramivir resulted in greater median virus titer reductions from baseline than placebo. The differences between peramivir and placebo were greatest at the Day 3 visits. While no overall dose response was appreciated, in the individual trials the greatest differences from placebo were noted for the highest peramivir doses, particularly at Day 3. In the integrated analysis, the difference in median virus titer reduction between the pooled peramivir group and placebo was also greatest at Day 3 (-1.48 versus -1.25 $\log_{10}$ $TCID_{50}$/mL, respectively).

Table 13: Time-Weighted Change from Baseline in TCID50 (log10/mL) by Treatment Group and Study Day (ITTI) - Placebo-Controlled Trials in Acute Uncomplicated Influenza

Clinical Trial	Study Day Visit	Time-Weighted Change from Baseline in log10 TCID50/mL				
			Peramivir 300 mg	Peramivir 600 mg	Peramivir Total	Placebo
0722T0621	Day 3	N	**N=87**	**N=87**	**N=174**	**N=85**
		Mean (SD)	-1.40 (0.77)	-1.53 (0.95)	-1.46 (0.87)	-1.24 (0.87)
		Median	-1.48	-1.5	-1.49	-1.15
		Min, Max	-3.5, 0.35	-4.94, 1.1	-4.94, 1.1	-3.85, 0.8
	Day 5	N	**N=95**	**N=93**	**N=188**	**N=97**
		Mean (SD)	-1.8 (1.03)	-1.93 (1.11)	-1.87 (1.07)	-1.69 (1.06)
		Median	-1.75	-1.85	-1.80	-1.65
		Min, Max	-5.33, 0.23	-5.67, 0.49	-5.67, 0.49	-5.64, 0.25
	Day 9	N	**N=95**	**N=93**	**N=188**	**N=97**
		Mean	-2.41	-2.51	-2.46	-2.32

		(SD)	(1.22)	(1.33)	(1.28)	(1.22)
		Median	-2.61	-2.44	-2.47	-2.16
		Min, Max	-5.99, -0.22	-6.54, 0.49	-6.54, 0.49	-6.23, -0.23
BCX1812-211/311	**Day 3**	N	**N=149**		**N=243** [a]	**N=123**
		Mean (SD)	-1.59 (0.87)		-1.60 (0.91)	-1.39 (0.85)
		Median	-1.63		-1.69	-1.38
		Min, Max	-3.75, 0.94		-3.94, 1.13	-3.88, 1.31
	Day 5	N	**N=150**		**N=244** [a]	**N=123**
		Mean (SD)	-2.06 (0.98)		-2.09 (1.03)	-2.03 (0.95)
		Median	-2.08		-2.16	-1.97
		Min, Max	-4.38, 0.5		-4.59, 0.88	-3.01, 0.22
	Day 9	N	**N=150**		**N=244** [a]	**N=123**
		Mean (SD)	-2.72 (1.09)		-2.73 (1.07)	-2.73 (0.97)
		Median	-2.67		-2.73	-2.82
		Min, Max	-5.28, 0.34		-5.28, 0.38	-5.05, 0.22
Integrated	**Day 3**	N	**N=236**	**N=87**	**N=417** [a]	**N=208**
		Mean (SD)	-1.52 (0.84)	-1.53 (0.95)	-1.54 (0.89)	-1.33 (0.86)
		Median	-1.5	-1.5	-1.48	-1.25
		Min, Max	-3.75, 0.94	-4.94, 1.1	-4.95, 1.13	-3.88, 1.31
	Day 5	N	**N=245**	**N=93**	**N=432** [a]	**N=220**
		Mean (SD)	-1.96 (1.02)	-1.93 (1.11)	-1.99 (1.05)	-1.88 (1.01)
		Median	-1.94	-1.85	-2	-1.84
		Min, Max	-5.33, 0.5	-5.67, 0.49	-5.67, 0.88	-5.64, 0.25
	Day 9	N	**N=245**	**N=93**	**N=432** [a]	**N=220**
		Mean (SD)	-2.6 (1.15)	-2.51 (1.33)	-2.6 (1.17)	-2.55 (1.01)
		Median	-2.63	-2.44	-2.62	-2.57
		Min, Max	-5.99, 0.34	-6.54, 0.49	-6.54, 0.49	-6.23, 0.22

a) Peramivir Total includes PRV 150 mg treatment group (not shown)
Source: created by clinical reviewer using the analysis virology dataset (ADVIR.xpt) - Integrated Summary of Efficacy (ISE)

When viral culture data from non-H275Y infected subjects in Study BXC1812-212 (N=62) were added to the integrated analyses, similar results were obtained; e.g. the median viral titer reduction at Day 3 for the pooled peramivir group was -1.5, compared with -1.25 for the pooled placebo group. Changes from baseline in absolute virus titer (not shown) were also consistent with results of the time-weighted TCID50 analyses.

Table 14 shows the proportion of subjects per arm shedding virus at each study visit for Studies 0722T0621 and BCX1812-211/311 as well as the integrated analysis. Only the 300 mg and 600 mg doses are shown for peramivir; however, the PRV 150 mg group is

counted in the peramivir totals for Study BCX1812-211 and the pooled analysis. It should be noted that the virology sampling schedule was not identical across trials and that not every subject had a sample collected at each time point.

In general, the proportion of subjects shedding virus was lower in the peramivir treatment groups than in the placebo group through the Day 3 visit. In the integrated analysis, the difference between the pooled peramivir group and placebo was greatest at Day 3 (40% versus 56%, respectively). There also appeared to be a dose response as evidenced by the Day 2 and 3 results for Study 0722T0621 and the integrated analysis. In both, the proportion of subjects shedding virus at Day 3 in the PRV 600 mg group was reduced by at least half compared with placebo, and was lower than in the PRV 300 mg treatment group. Although not shown, a similar but smaller dose response was noted between the 150 mg and 300 mg PRV dose groups in Study BCX1812-211/311. After Day 3, virus titers decreased rapidly in all treatment groups and no significant differences were noted between arms. No virus was detected in most subjects by the Day 9 visit.

Table 14: Percentage of Subjects with Detectable Virus Titer (TCID50) by Treatment Group and Study Day (ITTI) - Placebo-Controlled Trials in Acute Uncomplicated Influenza

Clinical Trial	Study Day Visit	Percentage of Subjects Shedding Virus (Detectable TCID50) (n/N) [a]			
		Peramivir 300 mg	Peramivir 600 mg	Peramivir Total	Placebo
0722T0621	Baseline [b]	N=96	N=95	N=191	N=97
	Day 2	84% (38/45)	67% (28/42)	76% (66/87)	85% (33/39)
	Day 3	37% (35/95)	26% (24/93)	31% (59/188)	52% (50/97)
	Day 5	10% (9/95)	10% (9/93)	10% (18/188)	13% (13/97)
	Day 9	0 (0/95)	1% (1/91)	1% (1/186)	0 (0/96)
BCX1812-211/311	Baseline [b]	N=151		N=245 [c]	N=124
	Day 2	82% (80/97)		81% (154/190)	95% (93/98)
	Day 3	44% (64/147)		47% (114/241)	60% (73/122)
	Day 5	22% (33/149)		24% (58/243)	21% (26/121)
	Day 9	5% (7/146)		7% (16/239)	8% (10/122)
	Day 9		3% (3/118)	3% (3/118)	2% (3/140)
Integrated	Baseline [b]	N=247	N=95	N=436 [c]	N=221

[redacted]	Day 2	83% (118/142)	67% (28/42)	79% (220/277)	92% (126/137)
	Day 3	41% (99/242)	26% (24/93)	40% (173/429)	56% (123/219)
	Day 5	17% (42/244)	10% (9/93)	18% (76/431)	18% (39/218)
	Day 9	3% (7/241)	1% (1/91)	4% (17/425)	5% (10/218)

a) n = number of subjects with detectable TCID50; N = number of subjects with available viral sample on study day
b) Baseline N = number of subjects with detectable TCID50 at baseline prior to initiation of study treatment.
c) Peramivir Total includes PRV 150 mg treatment group (not shown)
Source: created by clinical reviewer using the analysis virology dataset (ADVIR.xpt) - Integrated Summary of Efficacy (ISE)

No significant differences from placebo were noted in Study BCX1812-212 in the proportion of subjects shedding virus at any study visit, as would be expected a season with low NAI susceptibility.

Please refer to the Virology Review by Dr. Takashi Komatsu for further analyses of the virologic endpoints by influenza subtype and duration of symptoms.

Time to Resumption of Usual Activities

The endpoint of time to resumption of usual daily activities was a secondary one in Studies 0722T0621 and BCX1812-211/311; this endpoint was not assessed in Study BCX1812-212. Subjects were defined as having had resumption of usual activities if they had a self-assessment score of 10 on the visual analog scale or activity assessment for the ability to perform usual activities.

Table 15 provides the Kaplan-Meier estimates for the median time to resumption of usual activities for the integrated analysis. The median time was 11 days for subjects in the PRV 150 mg group; 8 days for subjects in the PRV 300 mg group; and 6 days for subjects in the PRV 600 mg group, compared with 9 days for subjects in the placebo group. While a dose response was noted, only the PRV 600 mg group (from Study 0722T0621) showed a significant difference compared with placebo. No difference was seen in Study BCX1812-211/311. As such, the reduction in time compared with placebo was only 1 day for the overall peramivir group in this analysis.

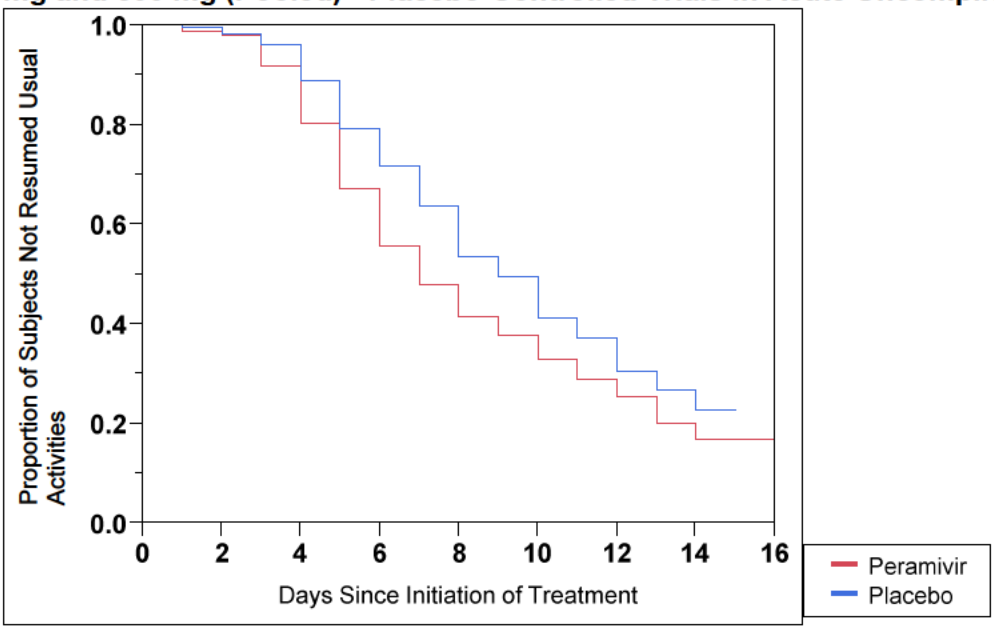
Table 15: Median Time to Resumption of Usual Activities by Treatment Group (ITTI) - Placebo-Controlled Trials in Acute Uncomplicated Influenza (Pooled)

Kaplan-Meier Estimate	Peramivir 150 mg	Peramivir 300 mg	Peramivir 600 mg	Peramivir Total	Placebo
N (number censored)	100 (40)	253 (58)	98 (11)	451 (109)	226 (56)
Median Time, days	11	8	6	8	9
(95% CI)	(9-13)	(7-9)	(6-7)	(7-9)	(8-10)
25% - 75%	7 - N/A	5 - 13	5 - 10	5 - 13	6 - 14

Source: created by clinical reviewer using the analysis efficacy time to event dataset (ADTTE xpt) - Integrated Summary of Efficacy (ISE)

When the PRV 150 mg dose group was excluded from the analysis, however, there was a clearer differentiation between peramivir and placebo, as demonstrated in Figure 5. Here the median time to resumption of usual activities was 7 days for the pooled PRV 300 mg and 600 mg groups, representing a two-day improvement over placebo.

Figure 5: Kaplan-Meier Curves for Resumption of Usual Activities (ITTI) - Peramivir 300 mg and 600 mg (Pooled) - Placebo-Controlled Trials in Acute Uncomplicated Influenza



Source: created by clinical reviewer using analysis efficacy time to event dataset (ADTTE.xpt) - Integrated Summary of Efficacy (ISE)

6.1.6 Other Endpoints

Influenza-Related Complications

Although the incidence of influenza-related complications (bronchitis, otitis, pneumonia, and sinusitis) was a secondary endpoint in Studies 0722T0621 and BCX1812-311, and an exploratory one in BCX1812-212, none of the protocols prospectively defined

objective criteria for the diagnosis of these conditions. Instead, the protocols included a checklist to prompt investigators to assess for signs and symptoms of influenza-related complications. As such, the incidence of these investigator-diagnosed conditions varied considerable between trials, from 2-3% in Study 0722T0621 to 19-20% in the BioCryst trials. However, no significant differences were observed between peramivir and placebo.

Change in Inflammatory Cytokines

Several investigators have tried to establish a correlation between cytokine release and influenza infection. In Study 0722T0621, change from baseline in IL-6 and TNF-α was a secondary endpoint. The amount of change per unit time was calculated from the time of screening up to the Day 14 visit. Only the amount of change in IL-6 in the PRV 600 mg group was significantly different from placebo. Significant differences in the amount of change in IL-6, TNF-α, or CRP varied by study day and peramivir dose, but no consistent pattern could be discerned. Moreover, the clinical significance of these findings is not clear.

Acetaminophen Use

Acetaminophen use was a pre-specified secondary endpoint in Study 0722T0621. As this was the trial that showed the greatest treatment benefit of peramivir over placebo, acetaminophen use in this trial was analyzed more closely. Moreover, the concomitant medications dataset for Study 0722T0621 contained acetaminophen dosage information, which the BioCryst datasets did not.

As shown in Table 16, by all measures, acetaminophen use was less in the peramivir treatment groups than in the placebo group.

Table 16: Acetaminophen Use in Study 0722T0621 (ITTI)

Acetaminophen Usage	Peramivir 300 mg N=99	Peramivir 600 mg N=98	Placebo N=100
Number of subjects, n (%)	67 (68%)	69 (70%)	77 (77%)
Total consumption (gm)	5.69	5.36	7.98
Mean consumption (mg)	849	776	1036
Min, Max (mg)	300, 3000	300, 2700	300, 4200
Number of doses, mean	2.7	2.6	3.5
Number of days, median	1.0	1.5	2.0

Source: Created by clinical reviewer using concomitant medications dataset (CM.xpt) - Study 0722T0621

Development of Resistance

Please refer to the Virology Review by Dr. Takashi Komatsu for detailed analyses of the resistance observed in the peramivir clinical development program.

In brief, the resistance analyses conducted by Shionogi were inadequate. For study 0722T0621, the sponsor only sequenced the NA gene of influenza viruses from subject specimens demonstrating pretreatment or post-treatment peramivir IC_{50} values that were greater than a threshold of a mean IC_{50} value + 3 standard deviations for NA inhibition activity. The utility of phenotypic analyses as a screen for resistance is suspect given the assay selection bias for wild-type strains when subject samples are amplified in cell culture prior to testing. Additionally, the type of substrate used may have affected the sensitivity of the assay. Lastly, a clinical cutoff has not been established for phenotypic assays. Another source of bias is the inability of the neuraminidase assay to detect resistance developing in the viral hemagglutinin. Shionogi did not genotype the HA in any of its Phase 2 trial samples. However, amino acid substitutions in the HA conferring reduced susceptibility to peramivir were selected in cell culture studies (see Section 4.2). Of note, these substitutions were selected in the absence of any resistance-associated amino acid substitutions in the NA.

For the BioCryst-sponsored trials, samples were genotyped based on the following criteria:

- Detectable influenza virus by cell culture or RT-PCR at Day 5 or later.
- Virus isolates with peramivir IC_{50} values 3x the baseline median using the NAI assay.
- For the hospitalized Studies BCX1812-301 and BCX1812-303: Virus isolates with a peramivir IC_{50} value <3x median baseline IC_{50} value with a last detectable RT-PCR at the last assessment that were not included in either of the other 2 subsets.

This nested RT-PCR-based assay has been validated for full length sequencing of NA and HA for influenza A/H1N1pdm09, A/H3N2 and B viruses.

The only influenza A/H1N1 amino acid substitution that developed in more than one subject was the NA H275Y substitution. In the placebo-controlled trials, 7 subjects in Studies 0722T0621 and BCX1812-211 developed the NA H275Y amino acid substitution while on treatment. Additionally, there were 2 subjects who had the H275Y substitution at baseline and 1 subject who had the H275Y substitution at Day 3 but the baseline sample was not genotyped. As expected, all of these isolates had reduced susceptibility to oseltamivir but not zanamivir. The median time to resolution of symptoms for these 10 subjects, however, was still 57 hours (mean 94.3 hours), suggesting a negligible impact of the H275Y substitution in this small cohort.

For subjects infected with influenza A/H3N2 virus, there were no amino acid substitutions that developed in more than one subject. The R292K substitution, conferring resistance to oseltamivir and zanamivir, developed in one subject (Subject BCX1812-211.461.052). This subject had a baseline viral load of 4.3 $\log_{10}$ $TCID_{50}$/mL at baseline, 2.3 $\log_{10}$ $TCID_{50}$/mL at Day 3 and <LLOQ at Day 5. The NA R292K amino acid

substitution was observed on Day 3. The IC_{50} value for peramivir in the neuraminidase inhibition assay was 0.19 nM at baseline and 1.13 nM at Day 5. Another subject in Study BCX1812-211 (Subject 004.002) had virus that developed the N294S neuraminidase resistance substitution, which confers resistance to peramivir. This subject had had a viral load of 5.75 $\log_{10}$ $TCID_{50}$/mL at baseline, and 1.5 $\log_{10}$ $TCID_{50}$/mL at both Days 3 and 5. The NA N294S substitution was observed on Day 5. The IC_{50} value for peramivir in the neuraminidase inhibition assay was 0.05 nM at baseline and 1.43 nM at Day 5. For the few subjects infected with influenza B virus, there were no amino acid substitutions that developed in more than one subject. No transmission of resistant virus among subjects who had treatment-emergent resistance was documented.

Data from 2 years of postmarketing surveillance in Japan following the approval of peramivir (RAPIACTA) have not identified any novel substitutions in circulating seasonal influenza strains that are associated with loss of susceptibility to peramivir.

The FDA virology reviewers also mapped the resistance-associated substitutions observed in virus isolates to determine if they occurred at known antigenic sites in the HA surface of influenza A and B viruses. All of the peramivir resistance-associated substitutions that emerged in H1N1 and H3N2 influenza virus populations led to changes in antigenic sites. The resistance-associated substitutions that emerged in the presence of peramivir in influenza B virus also mapped to the HA surface. There is a theoretical risk, therefore, that patients who fail peramivir treatment may propagate influenza strains with reduced susceptibility to influenza vaccine. This issue will need to be further evaluated; please the Virology review by Drs. Takashi Komatsu and Eric Donaldson for further details of possible postmarketing study considerations.

6.1.7 Subpopulations

For the subgroup analyses, an integrated approach was taken to evaluate the primary endpoint of TTAS. Some of the subgroups were very small and did not allow for meaningful conclusions to be made. Therefore, data from the PRV 300 mg and 600 mg treatment groups in the four placebo-controlled trials were pooled together for this analysis.

Overall there was a consistent numerical benefit of peramivir treatment with respect to resolution of symptoms across subgroups defined by region, age, gender, race, smoking status, influenza A virus subtype, symptom duration at baseline, and severity of illness. Nonetheless, as shown in Table 17, the greatest differences from placebo were noted in women, Asians, young adults (age 18-40 years), subjects with normal BMI, subjects with low initial symptom scores (<14), and subjects who presented for treatment within 24 hours of symptom onset. Perhaps owing to the small sample sizes, the efficacy of peramivir could not be demonstrated in Blacks, Hispanics, the elderly (age ≥ 65 years), the obese, subjects infected with influenza B, or subjects who

presented beyond 36 hours of symptom onset. As expected, peramivir was not effective in subjects infected with influenza A/H1N1 with the H275Y substitution. Current smoking status did not have a noticeable impact on peramivir efficacy.

Table 17: Median Time to Alleviation of Symptom by Subgroup Characteristics (ITTI) - Placebo-Controlled Trials in Acute Uncomplicated Influenza (Pooled Peramivir 300 mg and 600 mg)

Subgroup Characteristic		Number of Subjects (censored)		P-value*
		Kaplan-Meier Estimate Median Time to Alleviation of Symptoms		
		Peramivir	Placebo	
Overall		N=511 (55)	N=399 (41)	
		80	107	<0.0001
Sex	Female	N=251 (33)	N=200 (30)	
		84	126	<0.0001
	Male	N=260 (22)	N=199 (11)	
		79	94	0.0698
Age	18 to < 40 years	N=362 (33)	N=282 (29)	
		78	111	<0.0001
	40 to < 65 years	N=143 (19)	N=115 (12)	
		82	101	0.1976
	≥ 65 years	N=6 (3)	N=2 (0)	
		N/A	151	0.2733
Race	Asian	N=217 (13)	N=124 (12)	
		63	95	<0.0001
	Black	N=55 (12)	N=65 (7)	
		92	80	0.9676
	White	N=204 (24)	N=177 (18)	
		104	123	0.0554
	Other	N=35 (6)	N=33 (4)	
		135	109	0.7303
Ethnicity	Not Hispanic	N=294 (24)	N=197 (3)	
		67	107	<0.0001
	Hispanic	N=13 (5)	N=12 (2)	
		88	84	0.7836
	Unknown	N=204 (24)	N=190 (16)	
		94	112	0.6792
Region	Japan/SE Asia	N=197 (10)	103 (8)	
		60	85	<0.0001
	North America	N=169 (21)	N=142 (13)	
		94	107	0.2776
	Rest of World	N=145 (24)	N=154 (20)	

		113	126	0.4573
Smoking Status	No	N=379 (45)	N=305 (33)	
		87	113	0.0018
	Yes	N=132 (10)	N=94 (8)	
		67	96	0.0038
BMI	< 24.9	N=269 (29)	N=112 (21)	
		78	112	<0.0001
	25.0 - 29.9	N=140 (14)	99 (12)	
		76	104	0.0248
	> 30. 0	102 (12)	88 (8)	
		104	103	0.8959
Influenza Subtype	A/H1N1	N=188 (12)	N=110 (11)	
		66	96	0.0007
	A/H1N1(H275Y)	N=104 (12)	N=124 (11)	
		92	109	0.6636
	A/H3N2	N=148 (18)	N=106 (12)	
		78	114	0.0015
	A/Indeterminate	N=7 (1)	N=6 (3)	
		106	N/A	0.0523
	A+B	N=2 (1)	N=1 (1)	
		56	N/A	0.3173
	B	N=59 (9)	N=52 (3)	
		127	113	0.4007
Influenza Initial Composite Score	≥ 14	N=244 (35)	N=218 (30)	
		104	125	0.0150
	< 14	N=266 (19)	N=181 (11)	
		67	85	0.0051
Duration of Symptoms	0 to 12 hours	N=48 (4)	N=22 (2)	
		64	95	0.2642
	12 to 24 hours	N=186 (22)	N=154 (15)	
		75	106	0.0005
	24 to 36 hours	N=192 (14)	N=160 (15)	
		88	113	0.0522
	> 36 hours	N= 87 (15)	N=63 (9)	
		104	106	0.2533

[1]P-value was based on the Wilcoxon-Gehan statistic for the comparison of peramivir to placebo
Source: Created by clinical reviewer using with ADTTE and ADSL datasets - Integrated Summary of Efficacy (ISE)

The differences noted in race, region, and BMI were likely due to the fact that the efficacy results were largely driven by data from Study 0722T0621, a trial conducted entirely in Japan, and therefore some of these covariates may have been acting as

surrogates for other effects. As noted in Section 6.1.2, Japanese subjects tended to present earlier for treatment and had lower symptom scores at baseline than subjects in the BioCryst trials, which were conducted predominantly outside of Asia. It is unlikely that differences in weight or BMI between Japanese/Asians and other race/region subgroups accounted for the observed differences in efficacy as the results in the placebo arms were also vastly different between these subgroups. Further, population PK results revealed that, with the exception of renal function, there were no clinically relevant covariates (e.g., age, weight, gender, and race) that would influence peramivir exposure. (Please see the Clinical Pharmacology review by Dr. Leslie Chinn for further discussion of exposure covariates).

Medical Officer's Comment:
A postmarketing study to evaluate the efficacy of IV peramivir against influenza B infection is strongly recommended.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The development program of peramivir for the treatment of acute uncomplicated influenza evaluated three single doses: 150 mg, 300 mg, and 600 mg. The pharmacokinetics of IV peramivir support single-dose treatment. The efficacy results presented in Sections 6.1.4 and 6.1.5 suggest that the 150 mg dose of peramivir should not be considered further. However, no significant differences were observed between the 300 mg and 600 mg single doses with respect to the primary endpoint or most of the secondary endpoints analyzed.

The Applicant has proposed the 600 mg single dose of IV peramivir for the treatment of acute uncomplicated influenza, and justified selection of the 600 mg dose based on the following:

- In Study 0722T0621, a dose-ordered response was seen for viral shedding at Day 3. Per the Applicant, there was also a statistically significant superiority for viral load reduction ($log_{10}TCID_{50}$/mL) at Day 3 for the 600 mg dose, but not for the 300 mg dose.

- In the integrated analysis of the four placebo-controlled trials (ITTI population), there was a dose-ordered response for the primary endpoint of TTAS.

- A simulation study was conducted using the results of the PK model (see Section 4.4.2). The specific question asked was what fraction of the population would achieve twice the ET_{50} with single IV doses of 300 mg and 600 mg. Twice the ET_{50} (2x 21.8 hours = 43.6 hours) was chosen as being a practical clinical duration, given the typical duration of symptoms and the typical delay between onset of symptoms and start of treatment.

The results of the PK/PD simulation showed that compared to the 300 mg dose, the 600 mg dose resulted in more subjects exceeding the IC_{50} for the target duration in a typical influenza season (Study 0722T0621) and in a low NAI-susceptibility season (Study BCX1812-212), as shown in Table 18.

Table 18: Summary of PK/PD Report BCX1812-PKK-1

Study	GM IC_{50} (ng/mL)	Patients with target time above IC_{50} (%)	
		300 mg	600 mg
All	6.13	43.9	52.1
0722T0621	0.348	93.2	98.4
BCX1812-212	11.6	12.7	21.1

Abbreviations: GM = geometric means
Source: FDA Clinical Pharamacology reviewer

The FDA review team met to consider the available data to support the 600 mg dose over the 300 mg dose. Although the clinical significance of virologic endpoints is not clear, and the pharmacodynamically most responsive PK parameter for antiviral activity has not been established for NAIs, the review team concluded that the totality of the data favored the 600 mg dose. More importantly, no increased toxicity was observed with the 600 mg dose compared with the 300 mg dose, thus there was no clinical opposition to the selection of the higher dose. Please refer to the FDA Biostatics, Clinical Pharmacology, and Virology reviews for further analyses of dose-response relationships.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the adult clinical trials of peramivir in acute uncomplicated influenza, the primary endpoint was time to alleviation of influenza symptoms; i.e., time to onset of treatment effect. As such, the assessment of treatment response over time has been covered in Section 6.1.4. Since peramivir is to be given as a single dose, tolerance effects are not considered relevant.

To evaluate the persistence of efficacy, this reviewer analyzed the clinical trial data from the pivotal Study 0722T0621 to identify cases where influenza symptoms may have relapsed after the primary endpoint was met. Relapse was defined as the occurrence of a moderate or severe diary entry for at least one symptom post healing. Among the 279 subjects who reported alleviation of symptoms in this trial, 45 subjects (16%) were identified with relapse: PRV 300 mg 13%, PRV 600 mg 16%, and placebo 19%. The median time to relapse was generally the same between groups (3.5 days for the PRV 300 mg group and 3 days for the PRV 600 mg and placebo groups), with no differences in range (1 to 8-9 days). The majority of these subjects (60%) had cough as one of their

relapsed symptoms, with comparable incidence across treatment groups. Most subjects with relapse of cough rated their symptom as moderate. In addition, while subjects in the placebo group tended to have a greater number and variety of relapsed symptoms, most of the peramivir-treated subjects had recurrence of only one or two symptoms. Smoking status did not appear to correlate significantly with risk of relapse. As lingering cough is a typical finding following upper-respiratory tract infection, these findings are neither surprising nor do they necessarily suggest a loss of peramivir therapeutic effect. Please refer to the Biostatics Review by Dr. Thomas Hammerstrom for additional analyses of relapse post healing.

6.1.10 Additional Efficacy Issues/Analyses

One potential criticism of the efficacy review of IV peramivir for the proposed indication is the substantial reliance on a single Phase 2 clinical trial, conducted in a Japanese population. The efficacy results in Study 0722T0621, however, were considered very persuasive, with a one-sided P value of 0.0010 for the difference in the primary endpoint between the pooled peramivir group and placebo. Study 0722T0621was also an adequate and well-controlled multicenter trial in which no single study site provided an unusually large fraction of subjects and no single site was disproportionately responsible for the favorable effect observed. In addition, the effect of peramivir was consistent across multiple endpoints and subgroups in that trial, all of which would make the single trial adequate support for an effectiveness claim in accordance with the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*[11]. If that were not sufficient, the findings of Study 0722T0621 were further corroborated by the integrated efficacy analyses using data from the BioCryst IM trials. In the integrated analyses, the effect of peramivir was demonstrated across a more diverse population and was consistent across multiple subgroups defined by age, race, sex, or influenza subtype.

A comparison of peramivir efficacy to oseltamivir, an FDA-approved NAI for treatment of influenza, was attempted in Study 0815T0631. The evaluation of efficacy in that trial, however, was compromised by the predominance of a circulating influenza A/H1N1 virus strain with decreased NAI susceptibility. Antiviral activity against influenza A/H3N2 and influenza B in that trial, however, were comparable between peramivir and oseltamivir. Please see the Virology Review by Dr. Komatsu and the Biostatistics Review by Dr. Hammerstrom for further details regarding efficacy comparisons to oseltamivir.

Lastly, the proposed indication for peramivir assumes efficacy against influenza A and B viruses. The preclinical data suggests that influenza B is less susceptible than influenza A to peramivir, similar to the case with other NAIs. However, the number of subjects

[11] FDA guidance for industry, 1998, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

with influenza B infection in the placebo-controlled trials submitted in support of this application was very small, and no determination could be made regarding peramivir effectiveness against this influenza type. Labeling for RAPIVAB should indicate this limitation of the data. Additionally, a postmarketing commitment to further evaluate peramivir efficacy against influenza B should be considered (see Section 1.4).

7 Review of Safety

Safety Summary

The evaluation of peramivir safety in support of this application was based primarily on clinical trial data from five adequate and well-controlled Phase 2 and 3 trials conducted in adults with acute uncomplicated influenza: the Shionogi-sponsored Studies 0722T0621 and 0815T0631, both conducted in Asia using the IV formulation of peramivir, and the BioCryst Studies BCX1812-211, -311, and -212, conducted globally, including the United States but mostly excluding Asia, using the IM formulation. The Phase 1 Studies BXC1812-111 and -113 demonstrated the bioequivalence of the IM and IV formulations of peramivir, thus enabling use of data collected with the IM formulation to support the IV formulation. In addition, supportive safety data from a small noncomparative trial (N=44) of IV peramivir conducted in Japanese subjects with high-risk factors (Study 0816T0632) were used to evaluate the major safety results.

Although the safety analysis for this review focused on the above controlled Phase 2 and 3 trials, safety information from the overall peramivir development program was also taken into account. This included information from clinical trials conducted in hospitalized influenza patients and an open-label Japanese study in pediatric subjects. In addition, the postmarketing information regarding the safety of IV peramivir reported from Japan and safety information collected during the 2009 EUA and emergency IND experience was reviewed.

The methods used to assess safety in the individual trials, and in the integrated summary, were considered appropriate. For the FDA review, major safety results were analyzed for each trial independently because of the different formulations and doses of peramivir used in each, as well as differences in baseline demographics noted between trials. An integrated approach was taken for the analyses of supportive safety results and submission specific events of interest. For the integrated analyses, data from the five controlled trials were pooled for the 300 mg and 600 mg peramivir dose groups and compared to a pooled placebo cohort.

Across the five controlled trials in adults with acute uncomplicated influenza, a total of 1,399 subjects were exposed to at least one dose of peramivir. Doses ranged from 150 mg to 600 mg; mean and median duration of treatment was 1 day. The number of

subjects exposed to the proposed to-be-marketed 600 mg dose was 664 (b) (4) Although there were differences in baseline demographics between the trials, in general the subject populations were representative of the target population for the proposed indication. Nonetheless, elderly subjects, Hispanic subjects, and Black or African-American subjects were underrepresented in the safety population. Peramivir exposures, however, are not expected to be significantly different based on baseline covariates based on results of population PK studies.

Overall, peramivir was found to have an acceptable safety profile in adults with acute uncomplicated influenza, with no notable dose effect. One death was reported in a subject treated with IM peramivir 300 mg, but the cause of death (meningitis) was not considered related to study drug. Serious AEs were uncommon, occurring in 0.5% (7/1,441) of peramivir-treated subjects, including those in Study 0816T0632. The most common SAE was pneumonia/bacterial pneumonia, occurring in three peramivir-treated subjects; none of the SAEs was considered related to study drug. As peramivir was administered as a single dose, there were no reports of study drug discontinuations due to adverse events. Notably, there were no reports of dose interruptions or dose reductions because of infusion site reactions, hypotension, hypersensitivity, or anaphylaxis reactions. More subjects treated with peramivir dropped out of Studies 0815T0631 and 0816T0632 because of skin reactions (drug eruption, rash) compared to a cohort of subjects treated with oseltamivir (3 [0.2%] versus 0), but none of these rash events was serious.

Significant or severe AEs (DAIDS Grade ≥ 3) were reported in 2-8% of peramivir-treated subjects depending on the trial; the incidence of these events in the peramivir treatment-groups was generally comparable to or lower than those in the control groups (placebo or oseltamivir). No distinct trends were noted for these AEs by MedDRA hierarchy terms. These AEs also generally tended to represent laboratory test abnormalities, which were reported more frequently as AEs by Shionogi investigators. There was one severe event of hypersensitivity in a woman treated with IM peramivir 300 mg that was considered possibly related to study drug; the event occurred on Day 4-5 after study drug administration, was not serious, and resolved with medical therapy (prednisone, diphenhydramine, and famotidine).

Submission specific events of interest were analyzed as part of this safety review and included: neuropsychiatric events, rash, hypersensitivity, liver enzyme abnormalities, and hemorrhagic colitis, renal toxicity, leukopenia/neutropenia, muscle injury, orthostatic hypotension/shock, and convulsion. These events were selected based on observations from the peramivir development program, the postmarketing experience with IV peramivir (RAPIACTA) in Japan, and safety labeling for other drugs in the NAI drug class (Tamiflu, Relenza). Events were analyzed by the Applicant and FDA using broad and narrow Standard MedDRA Queries (SMQs) and selected MedDRA Preferred Terms. Based on clinical trial data from the five controlled trials, there was no compelling evidence to suggest an association between peramivir and increased risk of

any of these specific events. Many of the events identified had alternative etiologies or were confounded, or their incidence was comparable to that of the comparator groups. That said, the laboratory data suggest there might be a mild increased risk of transaminitis associated with peramivir use, but there was no evidence of drug-induced liver injury. There were no cases consistent with Hy's Law. Muscle effects, when observed, tended to be mild to moderate and related to the IM formulation of peramivir. Likewise, orthostatic hypotension/shock events were related to the IM injections and tended to be vasovagal in nature.

Neuropsychiatric events occurred in less than 2% of peramivir-treated subjects in the five controlled trials and at comparable incidence as in the pooled placebo cohort. There were no events reported in any of the adult trials of acute uncomplicated influenza consistent with delirium, suicidality, or the type of abnormal behaviors described in the oseltamivir postmarketing experience. However, there were reports from Japan of abnormal behavior observed in children treated with IV peramivir, both in an uncontrolled pediatric trial and in the postmarketing setting. Given the uncontrolled nature of these reports, it is unclear if a true relationship exists. Nonetheless, labeling for peramivir should contain language in Warnings and Precautions regarding these events, consistent with that of other NAI drugs.

Rash events were noted in approximately 2% of peramivir-treated subjects (compared to 1% with placebo and 0.5% with oseltamivir). None of these events was serious or resulted in any action being taken, other than pharmacological intervention for one case each of urticaria and pruritus. Severe cutaneous adverse reactions were not reported in any of the six adult trials in acute uncomplicated influenza; however, there was one case of multiforme erythema reported in a critically-ill subject in one of the hospitalized trials of peramivir. The event was mild and not serious and causality was heavily confounded. In addition, there was one report of Stevens-Johnson syndrome and two of exfoliative dermatitis reported in postmarketing in Japan for which a role of peramivir could not be excluded. Labeling for peramivir should include language in Warnings and Precautions regarding serious skin reactions, consistent with labeling for other NAI drugs.

The most common clinical adverse events noted with peramivir use in the five controlled trials were diarrhea, nausea, vomiting and dizziness, but only diarrhea occurred at a marginally greater rate than placebo (8% versus 7%, respectively). These events tended to occur early, with mean time to onset of 3 days and median duration of one week. Their incidence and time-dependency were comparable to those seen in the control groups. These AEs have also been commonly reported in postmarketing with IV peramivir.

Based on the clinical laboratory data, peramivir may have a marginal effect on leukocyte and neutrophil counts compared with placebo, but these tended to be mild to moderate and short-lasting. Otherwise, peramivir did not have any significant effects on other

laboratory parameters evaluated, including hemoglobin, platelet counts, serum creatinine, and other chemistry tests. Peramivir also did not have a clinically significant effect on vital signs or electrocardiogram tests. The results of a thorough QT study suggested that peramivir at therapeutic or supratherapeutic doses was not associated with any conduction abnormalities or increased risk of adverse events.

No notable safety differences were noted based on age, race, or sex in the five controlled trials, although there were limitations to the analyses because of small sample sizes in some of the subgroups, as previously noted. Phase 1 pharmacokinetic and safety trials conducted in healthy elderly subjects and subjects with renal impairment demonstrated an acceptable safety profile of peramivir in these populations and have not revealed any new safety signals. Peramivir dosing recommendations for patients with renal impairment, however, will likely include a dose reduction due to anticipated systemic exposures 4- to 5-fold higher than those observed in adults with normal renal function. Phase 1 trials of peramivir with oseltamivir, rimantadine, probenecid, or oral contraceptives did not reveal any significant drug interactions, consistent with the pharmacology of the drug.

As a small molecule, there is minimal potential for immunogenicity with peramivir. Peramivir was not mutagenic or clastogenic in a battery of genotoxicity studies nor carcinogenic in a rat oral carcinogenicity study; no malignancies have been reported in the adult clinical trials.

Peramivir use in women who are pregnant or breastfeeding may be considered if the potential benefit outweighs any potential risk. There are no adequate and well controlled trials of peramivir use in pregnancy; however, data in rats demonstrated that peramivir did not produce maternal toxicity or embryotoxicity at doses of up to 600 mg/kg, which is approximately 9-fold greater than the proposed 600 mg dose in humans. From all available sources, i.e., the whole of the peramivir development program as well as the EUA and postmarketing experiences, there have been approximately 13 reports of pregnancy in women exposed to peramivir. Outcomes were available for 10 of these and none reported any suspected fetal anomalies. Peramivir will be classified as Pregnancy Category C in labeling. Studies of peramivir in rats have demonstrated that peramivir is excreted into breast milk at levels below the mother's plasma drug concentration. Although it is not known if peramivir is excreted into human breast milk, peramivir has been used safely in a small cohort of infants less than 1 year of age in the Japanese pediatric trial.

Review of the peramivir safety information from the clinical trials in hospitalized patients, the 2009 EUA experience and the Japanese postmarketing experience did not reveal any new safety signals that were not already noted in the clinical development program for the indication under current review, or that have not already been labeled for other neuraminidase inhibitor drugs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evaluation of IV peramivir safety was based primarily on data from the pivotal trial conducted by Shionogi, Study 0722T0621, and supported by data from the three BioCryst trials of IM peramivir (Studies BCX1812-211, -311, and -212). For this review, safety in each trial was evaluated separately, except for Studies BCX1812-211 and -311, which were pooled together as described in Section 6.1.1. Data from the IM peramivir trials were considered suitable to support the IV formulation following FDA inspection of Study BCX1812-113, a Phase 1 trial that evaluated the relative bioavailability of 600 mg peramivir administered IM versus IV in healthy adult subjects (see Section 4.4.3).

In addition, data from the Shionogi Study 0815T0631 were reviewed as part of the integrated safety analysis as this trial also evaluated the IV formulation of peramivir in adults with acute uncomplicated influenza. Subject demographics and disposition for this trial are included in the Appendices (Table 46 and Table 47).

Safety findings from the BioCryst trials in hospitalized patients (Studies BCX1812-201, -301, and -303) and the Shionogi Study 0816T0632 in high-risk subjects were taken into consideration if they were pertinent to the analysis, but in general these trials were not relied upon greatly to evaluate safety due to the use of different dosing regimens and presence of potentially confounding factors associated with a more seriously ill population (e.g., severity of influenza illness, comorbid conditions, and concomitant therapies). Safety in the Japanese pediatric trial (Study 0918T0633) was reviewed separately in Section 7.6.3, but general safety findings were incorporated into the integrated analysis whenever relevant to the adult indication.

7.1.2 Categorization of Adverse Events

Adverse events were appropriately categorized by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) standardized criteria. For the Integrated Summary of Safety (ISS), AEs were coded using MedDRA version 12.1; however, the individual trials used different versions of MedDRA. For the FDA safety review, MedDRA version12.1 was used for the MAED review of individualized and pooled trial safety data (see Section 7.1.3).

As per the Statistical Analysis Plan (SAP) for the ISS, agreed upon at the pre-NDA meeting, treatment-emergent AEs (TEAEs) were defined as any event reported in the CRF that occurred on or after the initiation of study drug and up to 28 days following discontinuation of study drug. Treatment-emergent laboratory toxicities were defined as laboratory abnormalities reported post-dosing with a toxicity grade greater than

baseline. For both TEAEs and laboratory abnormalities, the DAIDS Toxicity Grading Table was used for grading of severity.

The mapping of verbatim terms (AETERM) to MedDRA Preferred Terms (AEDECOD) was assessed for all AEs in Studies 0722T0621, BCX1812-212 and -311 and found to be acceptable.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Because of differences in peramivir formulation, baseline subject characteristics, influenza seasons, and disease severity among the four placebo-controlled trials of acute uncomplicated influenza (see Section 6.1.2), each trial was reviewed separately for the major safety analyses (i.e., deaths, serious AEs, AEs leading to discontinuation, and significant AEs), except for Studies BCX1812-211 and -311, which were pooled together for reasons previously noted.

For the analyses of submission-specific AEs of interest, common AEs, and supportive safety results, pooling across the five controlled trials (including Study 0815T0631) was done to augment sample size and improve precision when estimating AE incidence. Since the efficacy analyses determined that 150 mg dose of peramivir is not clinically relevant, these integrated safety analyses were based on pooled data from the 300 mg and 600 mg peramivir dose groups, using a cohort of pooled placebo subjects from the four placebo-controlled trials (Studies 0722T0621, BCX1812-211, -311, and -212) as the main comparator. Data from subjects treated with oseltamivir in Study 0815T031 were also sometimes included for comparison purposes.

Study 0816T0632 was excluded from the pooled analyses due to differences in subject population and dosing regimens; however, this trial was reviewed with Study 0815T0631 for the major safety analyses.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Across the six trials of peramivir in adults with acute uncomplicated influenza, a total of 1,441 subjects received at least one dose of peramivir (Table 19). The cumulative peramivir dose exposure ranged from 150 mg to 2400 mg, with a median of 300 mg. The number of subjects who received the proposed to-be-marketed 600 mg single dose was 685; however, the number of subjects with peramivir exposure ≥ 600 mg was 698.

Duration of peramivir treatment ranged from 1 day to 5 days, with a median and mean exposure of 1 day. In the five controlled trials in acute uncomplicated influenza (Studies

0722T621, 0815T0631, BCX1812-211, - 212, -311), subjects were administered a single dose. In Shionogi Study 0816T0632, which enrolled high-risk subjects, multiple days of therapy were allowed. The most common dosing period in the latter trial was 2 days, but three subjects were treated for 3 days, one subject for 4 days, and one subject for 5 days.

Table 19: Peramivir Exposure - Adult Clinical Trials of Acute Uncomplicated Influenza (Safety Population)

Study Population	Type of Control	Study ID	Peramivir 150 mg	Peramivir 300 mg	Peramivir 600 mg	Placebo
Acute Uncomplicated Influenza	Placebo	0722T0621		99	99	100
		BCX1812-211	108	111		109
		BCX1812-311		54		25
		BCX1812-212			200	202
		Total	108	264	299	436
	Oseltamivir	0815T0631		363	365	
	Controlled Trials Total		108	627	664	436
With High Risk Factors	No Control	0816T0632		21	21	
OVERALL TOTAL			108	648	685	436

Table reflects exclusion of 17 subjects (Sites 60 and 700) in Studies BCX1812-211 and -311.
Source – created by clinical reviewer using analysis subject level dataset (ADSL.xpt) - Integrated Summary of Safety (ISS)

Although there were some differences in subject demographics between trials, in general the subjects evaluated were representative of an adult population with acute uncomplicated influenza. As noted in Section 6.1.2, certain subgroups were underrepresented, namely the elderly, Hispanics and Blacks or African-Americans.

7.2.2 Explorations for Dose Response

Most of the clinical trials used in the safety review evaluated more than one peramivir dose. This reviewer evaluated dose response relationships for the major safety results and submission specific events of interest (see Section 7.3.5). As will be noted throughout this review, there were no notable or consistent differences in incidence or severity of TEAEs across the range of peramivir doses evaluated. Given the lack of a dose-safety response, and the linearity and dose-proportionality characteristics of peramivir PK (see Section 4.4.3), exposure-safety response analyses were not done. A

thorough QTc study with peramivir single doses up to 1200 mg showed no effects on cardiac conduction or increased frequency of AEs (see Section 7.4.5).

7.2.3 Special Animal and/or In Vitro Testing

Appropriate preclinical testing was performed as summarized in Section 4.3 of this review. Please refer to the Pharmacology-Toxicology Review by Dr. Kuei-Meng Wu for additional details.

7.2.4 Routine Clinical Testing

Routine clinical testing was performed at pre-specified regular intervals during the pivotal Phase 2 trial and supportive Phase 2/3 trials. The frequency and scope of testing was considered adequate. Safety assessments primarily included physical examinations, vital sign measurements, clinical laboratory testing, and ECG tests (IV peramivir trials only). Additional testing was performed as indicated in the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to Section 4.4.2 and 4.4.3, respectively, for discussion of the PD and PK assessments of peramivir. Significant drug interactions with peramivir are considered unlikely given the drug is not a substrate or inhibitor of P-glycoprotein mediated transport and does not exhibit any interactions with cytochrome P450 enzymes. Drug interaction trials were conducted with peramivir and representative anti-influenza drugs (oseltamivir and rimantadine), as well as with probenecid and oral contraceptives; refer to Section 7.5.5 for discussion of the study results. Also, refer to the Clinical Pharmacology review by Dr. Leslie Chinn for additional discussion of the peramivir metabolic, clearance and interaction workup.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant's efforts to identify AEs specific to the NAI drug class were adequate. The safety profiles of the currently approved NAIs (see Section 2.4) were carefully considered when selecting the safety analyses to be performed. Specifically, the Applicant and FDA conducted detailed analyses of rash and serious skin reactions, neuropsychiatric events, hypotension/shock, hypersensitivity, liver enzyme abnormalities, hemorrhagic colitis, leukopenia/neutropenia, infusion site reactions, and muscle injury based on the AE profiles of other NAI drugs (see Section 7.3.5). No new safety findings were noted during the review of peramivir that would be of relevance to other agents in the NAI drug class.

7.3 Major Safety Results

7.3.1 Deaths

Clinical Trials

Across the six Phase 2/3 clinical trials in adults with acute uncomplicated influenza, there was only one death (noted in Section 6.1.3). The subject's narrative is as follows:

> **Subject 653022** was a 46-year-old South African female treated with 300 mg IM peramivir in Study BCX1812-211. She reported onset of influenza symptoms 36-48 hours before Screening. Her past medical history was notable for mitral valve prolapse, intrapapillary ductal carcinoma of the breast, treated with radiotherapy, and sinusitis. At Screening, she appeared acutely ill with nausea, nasal congestion, myalgia, vomiting, pharyngitis, and bilateral rhonchi. RAT was positive for influenza A (later confirmed by PCR). She reported severe sore throat, cough, aches and pains, and headache and rated her ability to perform usual activities at 3 on a scale of 0-10. Baseline laboratory tests were generally within normal limits. Her self-measurement of temperature on Day 1 post-treatment showed that fever was not present. She was seen in clinic on Days 3, 5, and 9 where she reported gradual overall improvement, except for nasal congestion, cough, and aches and pains, which persisted. Her laboratory data and vital signs were stable at follow-up visits and her ability to perform usual activities progressively improved. The Investigator made presumptive diagnoses of sinusitis and bronchitis on Days 5 and 9. She reported mild headache on Day 9.
>
> The subject was seen for an unscheduled study visit on the morning of Day (b) (6) for complaints of headache and vomiting. She was noted to be "a bit disoriented", but influenza symptoms were better and there was no report of fever. Vital signs were stable. She was treated empirically with intramuscular diclofenac 75 mg and ketorolac 20 mg for possible migraine headache. The subject's husband telephoned later that same day stating the subject continued to complain of headache and was now more disoriented. The Investigator made a home visit and found her to be semi-comatose and restless, with shallow respirations. Vital signs were stable but pupils were 3 mm and non-reactive and neck stiffness was present. The Investigator administered midazolam and intubated the subject before she was transported by ambulance to a local hospital approximately 48 km away. The subject's vital signs remained stable during transport.
>
> Upon arrival at the hospital, the subject was admitted to the ICU where her temperature was 38.3°C and heart rate was 145/min. At this point, she was comatose and unresponsive. Left hemiparesis was noted as well as decorticate movements, ocular deviation, and a stiff neck. CT scan of the brain reportedly showed severe pansinusitis, increased intracranial pressure, and no abscess or infarct. Laboratory data showed WBC of 9.05 ($x10^3/mm^3$) with 91% neutrophils, hemoglobin 13.8 g, platelets 198K, creatinine slightly elevated, and bicarbonate decreased. A portable chest X-ray was reported as normal. Treatment with IV ceftriaxone, IV Solucortef, IV Decadron, and chloramphenicol was initiated for presumptive meningitis and mechanical ventilation was instituted. Shortly thereafter, the left pupil was noted to be dilated to 5 mm and not

reactive. This was followed in rapid succession by hypotension, bradycardia, and cardiac arrest. Resuscitation was attempted, but ventricular tachycardia ensued and pupils became fixed and dilated. Cardiac asystole followed and further resuscitation was not attempted. The subject's family declined autopsy.

Blood cultures (likely obtained after the administration of ceftriaxone) were negative for aerobic and anaerobic bacterial growth at 24 hours and 5 days. No cerebrospinal fluid was obtained pre-mortem due to the increased intracranial pressure. An independent radiology review of the cranial CT and chest X-ray showed no hydrocephalus or mid-line shift of the brain, but did show maxillary and ethmoid sinusitis with an air-fluid level in the right maxillary sinus and minimal mucosal thickening in the sphenoid sinus. The portable chest film suggested air space disease at the left base in the retrocardiac area.

The Investigator's assessment of the relationship of the SAE (meningitis) and outcome (death) to study drug was "unlikely related."

Aside from this one death, no other deaths were reported in any of the clinical trials of peramivir in acute uncomplicated influenza, including the Japanese pediatric trial. There were no deaths in the Phase 1 trials.

In the clinical trials of hospitalized patients with influenza (Studies BCX1812-201, -301, and -303), a total of 27 deaths were reported, 24 in peramivir-treated subjects (4% [24/585]) and three in placebo-treated subjects (2% [2/134]). Two of these placebo-treated subjects received oseltamivir as part of their standard of care. Also, 22 of the peramivir-treated subjects were in Study BCX1812-303, the open-label trial of IV peramivir that took place during the 2009 global influenza A/H1N1 pandemic. The most common causes of death in peramivir-treated subjects were respiratory failure (6 subjects), acute respiratory distress syndrome (ARDS) (5 subjects), and septic shock (4 subjects). In most cases, the cause of death was related to progressive influenza disease or complications thereof. None of the deaths was considered related to study drug by the investigators.

Table 20 provides a listing of all deaths reported in the peramivir development program.

Table 20: Deaths Listing - Peramivir Development Program

Subject	Country	Age	Sex	Dose (mg)	Time (Days)		Cause of Death	Related to Study Drug?
					On therapy	Post-treatment		
BCX1812-211								
653-002	South Africa	46	F	300 IM	1	(b) (6)	Meningitis	No
BCX1812-201								
607-002	South Africa	60	F	400 IV QD	2		Viral myocarditis	No
BCX1812-301								
379-011	Israel	63	M	PBO [a]	5		Respiratory arrest	No

						(b) (6)		
652-001	South Africa	60	F	600 IV QD	10		ARDS Staphylococcal Infection	No
725-001	United States	35	F	PBO [a]	5		Respiratory failure Septic shock Acute kidney injury	No
837-001	India	47	M	PBO [b]	5		Multiorgan disorder Pneumonia Septic Shock	No
BCX1812-303								
122-001	United States	61	M	100 IV QD [c]	2		ARDS	No
131-001	United States	53	F	600 IV QD [d]	9		Cardiac arrest Cardiac failure congestive	No
132-003	United States	28	F	600 IV QD	10		ARDS	No
132-008	United States	72	M	600 IV QD	9		Colitis Pseudomonal bacteraemia	No
138-002	United States	18	M	600 IV QD [e]	4		Hypoperfusion Sepsis Rhabdomyolysis Cardiac failure	No
143-004	United States	26	M	600 IV QD	10		End stage cystic fibrosis	No
151-005	United States	73	F	300 IV BID	2		Respiratory failure	No
153-013	United States	59	M	600 IV QD	10		Pulmonary embolism	No
167-001	United States	58	M	600 IV QD	4		Septic shock Cerebrovascular accident	No
170-001	United States	80	F	150 IV QD [f]	10		Retroperitoneal hemorrhage	No
176-002	United States	46	F	300 IV QD	5		Drug overdose	No
189-001	United States	67	F	300 IV QD	1		Meningococcal bacteraemia	No
191-008	United States	50	F	600 IV QD	5		Respiratory failure Cerebrovascular accident	No
310-004	United States	45	M	600 IV QD	10		Pneumonia necrotizing Renal failure	No
310-008	United	55	F	600 IV	10		Septic shock	No

						(b) (6)		
	States			QD			Respiratory failure	
							Non-Hodgkin's lymphoma	
							Pulmonary hemorrhage	
312-001	Canada	58	F	300 IV BID	10		Respiratory failure	No
407-001	Mexico	33	M	300 IV BID	10		Respiratory failure	No
							Interstitial lung disease	
							HIV infection	
407-002	Mexico	52	M	300 IV BID	9		Pneumonia	No
							Respiratory failure	
414-005	Mexico	43	M	600 IV QD	2		Septic shock	No
							Renal failure	
							ARDS	
414-008	Mexico	32	F	300 IV BID	1		Sepsis	No
							ARDS	
509-002	Australia	73	M	300 IV BID	5		Septic shock	No
509-003	Australia	67	F	150 IV QD [g]	5		Multiorgan failure	No
							Sepsis	
							Respiratory failure	

Abbreviations: ARDS = acute respiratory distress syndrome; BID = twice a day; PBO = placebo; QD = once daily

[a] Subjects 379-011 and 725-001 in BCX1812-301 were randomized to placebo but received oseltamivir as part of standard of care.

[b] Subject 837-001 in BCX1812-301 was randomized to placebo but did not receive any antivirals as part of standard of care.

[c] Subject 122-001 in BCX1812-303 was randomized to 600 mg IV peramivir, but dose was reduced to 100 mg/day due of renal insufficiency.

[d] Subject 131-001 in BCX1812-303 was randomized to 600 mg IV peramivir, but due of renal insufficiency dose was reduced to 150 mg/day on Day 3, and then to 15 mg/day while on hemodialysis (Days 5-8).

[e] Subject 138-002 in BCX1812-303 was randomized to 600 mg IV peramivir, but due of renal insufficiency dose was reduced to 150 mg on Day 2, and then to 100 mg/day on Days 3-4.

[f] Subject 170-001 in BCX1812-303 was randomized to 600 mg IV peramivir, but due to renal insufficiency subject actually received 150 mg/day throughout the study.

[g] Subject 509-003 in BCX1812-303 was randomized to 600 mg IV peramivir, but due to renal insufficiency dose was reduced to 150 mg on Day 1, and then to 100 mg/day on Days 2-5.

Source: Integrated Safety Summary (ISS) and clinical study reports (CSRs) and narrative summaries for Studies BCX1812-211, -201, -301, and -303.

Postmarketing Experience

In a post-approval observational surveillance study conducted in Japan between October 2010 and February 2012, no deaths were observed with use of RAPIACTA (IV peramivir) among adult (N=1,174) or pediatric (N=1,254) patients, nor have any deaths been reported in an ongoing observational study (initiated January 2010) in adult or pediatric patients with high-risk factors (N=759).

Spontaneous AE reporting collected by Shionogi (from marketing approval January 13, 2010 to data cut-off September 30, 2013) included four fatal cases, including two events of sudden death, one in a 50-year-old man and one in a 92-year-old woman; in both cases, the patient died within (b) (6) days of treatment. No autopsies were performed and the cases were confounded by underlying comorbidities. Please See Section 8 for more details of the peramivir postmarketing experience in Japan.

In South Korea, peramivir is currently allowed for use only as part of a safety surveillance protocol. There have been 468 patients treated with peramivir based on data collected from approval on August 13, 2010 through the 2012-2013 influenza season. Two deaths have been reported in adults treated with IV peramivir: one in a 98-year-old female (cause of death: pneumonia) and one in a male of unknown age (cause of death: multiorgan failure). Further details were not provided.

Emergency IND

During the 2009 H1N1 influenza national emergency, peramivir IV was made available by BioCryst for treatment of influenza in critically ill hospitalized patients in the United States under the FDA's emergency IND regulations. Between April and October of 2009, IV peramivir was administered to a total of 31 critically ill patients. These 31 patients had confirmed or presumed influenza A/H1N1pdm09 infection, but most did not have any underlying health conditions prior to influenza infection. Fatal outcomes were reported for 12 patients (39%) and the most frequent cause of death was respiratory failure or ARDS that was frequently accompanied by other organ dysfunction.

Emergency Use Authorization

As noted in Section 2.6, on October 23, 2009, the FDA issued an EUA for use of IV peramivir in certain patients hospitalized with influenza A/H1N1pdm09 virus infection. Approximately 1,274 hospitalized patients received IV peramivir through the EUA program. FDA received reports on 344 patients, including 28 children and 3 pregnant women. Many of these patients were critically ill, and 41% were on mechanical ventilation, while 19% were on renal replacement therapy. A total of 206 deaths were reported to FDA, including 53 patients (15% of the total study population) with an outcome of death coded as an AE. None of the deaths were attributed to peramivir by

the reporting physician, and most deaths occurred among patients who were obese, immunosuppressed, or had hypertension.[12]

In a case series of critically ill 2009 H1N1 influenza patients reported from two ICU networks, 31 adult and 21 pediatric patients received peramivir, primarily under the EUA. Mortality rates of 71% (adult) and 48% (pediatric) were reported in peramivir-treated patients; mortality in non-peramivir treated patients was 24% (adult) and 9% (pediatric). Although mortality rates in this case series were higher in peramivir-treated patients, direct comparisons are not reliable because according to the terms of the EUA peramivir was restricted to patients not responding to approved antivirals or for whom drug delivery via an IV route was considered appropriate due to other circumstances. Therefore, the conditions of the EUA dictated that peramivir was given to more seriously ill patients or patients who had progressed while receiving other NAIs, and thus did not allow for an adequate control group to compare outcomes.[13]

Another case series published by the California Department of Public Health described 57 critically ill patients treated with peramivir during the 2009 influenza A H1N1 pandemic under the EUA. In this series, patients treated with peramivir had a mortality rate of 51%. This study lacked a matched comparator group; however, patients treated with peramivir were more likely to die than patients treated with another NAI. On the other hand, peramivir-treated subjects in this series were also more likely to have adverse predictors of outcome, including a higher incidence of acute renal failure. The death rate among peramivir-treated patients was higher in this study compared to other studies in which patients received peramivir prior to the EUA, likely resulting from a higher prevalence of risk factors and comorbidities.[14] As with other reports related to the EUA experience, the most common reasons for treatment with IV peramivir were lack of response to oral or inhaled antivirals and suspected malabsorption, creating a selection bias that favored administration of peramivir in more seriously ill patients.

The high peramivir mortality rate reported in the above two series differs from the observed mortality in Study BCX1812-303, which also enrolled subjects during the 2009-2010 influenza A/H1N1 pandemic. In this prospective randomized trial in hospitalized patients, all subjects received IV peramivir and administration was not restricted to the conditions of the EUA (see Section 5.3 for further details). The overall mortality in this trial was 10% (22/230 total enrolled) and 15% for subjects admitted to the ICU at enrollment, both of which were less than the death rates observed in ICU patients not treated with peramivir (24%) in the first case series described above.

[12] Sorbello A, Jones S, Carter W, Struble K, Boucher R, Truffa M, et al. Emergency use authorization for intravenous peramivir: evaluation of safety in the treatment of hospitalized patients infected with 2009 H1N1 influenza A virus. Clin Infect Dis. 2012; 55:1-7.
[13] Fry A, Perez A, Finelli L. Use of intravenous neuraminidase inhibitors during the 2009 pandemic: results from population-based surveillance. JAMA 2011; 306:160-2.
[14] Louie J, Yang S, Yen C, Acosta M, Schechter R, Uyeki T. Use of intravenous peramivir for treatment of severe influenza A (H1N1)pdm09. PLoS ONE 2012; 7(6):e40261.

In addition to the United States, IV peramivir has also been used in other countries under emergency situations, including Israel, Australia, Mexico, and Hong Kong. Three fatalities were reported in Israel. No further details are available.

7.3.2 Nonfatal Serious Adverse Events

This section highlights the nonfatal SAEs observed in the Phase 2/3 trials in adults with acute uncomplicated influenza. There were no SAEs in the Phase 1 trials.

Overall, SAE incidence was low across all treatment groups in the six adult trials of acute uncomplicated influenza (placebo- and non-placebo controlled), with similar rates between the peramivir groups (0.5% [7/1453]) and the two control groups (placebo 0.5% [2/442]; oseltamivir 0.5% [2/365]). No peramivir dose effect was noted in the incidence of SAEs. Pneumonia was the most frequently reported SAE in peramivir-treated subjects (2 subjects, 0.1%). None of the SAEs in peramivir-treated subjects was considered related to study drug by the investigators.

Phase 2/3 Placebo-Controlled Trials in Acute Uncomplicated Influenza

Study 0722T0621

No SAEs were reported in this trial.

Studies BCX1812-211/311 and -212

Across the three BioCryst trials of IM peramivir, three SAEs were reported in three subjects (Table 21). One subject received peramivir IM 300 mg (Subject 653-022 in Study BCX1812-211 – see Section 7.3.1); the other two received placebo. None of the three SAEs was considered related to study drug. No SAEs were reported in Study BXC1812-311. The incidence of SAEs, therefore, was 0.2% (1/473) among all subjects treated with IM peramivir.

Table 21: Serious Adverse Events - Studies BCX1812-211, -311, and -212

Trial	Subject	Treatment	SAE	Toxicity Grade	Related	Outcome
BCX1812-211	653-022	Peramivir 300 mg IM x 1	Meningitis	4	Unlikely related	Death
	056-032	Placebo	Pyelonephritis	3	Not related	Resolved
BCX1812-212	309-151	Placebo	Disseminated tuberculosis	3	Not related	Resolved

Source: adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

Phase 3 Non-Placebo Controlled Trials in Acute Uncomplicated Influenza

In Studies 0815T0631 and 0816T0632, eight SAEs were reported in eight subjects (Table 22). Six SAEs were reported in Study 0815T0631 and two in Study 0816T0632 in high-risk subjects. Six SAEs were in the peramivir groups; the other two were in the oseltamivir group. All SAEs were DAIDS Grade 2 or 3. One SAE of 'vomiting' in an oseltamivir-treated subject was considered possibly related to study drug; otherwise none of the SAEs was considered related to study drug.

Table 22: Serious Adverse Events - Studies 0815T0631 and 0816T0632

Serious Adverse Event	Number of Subjects (%)		
	Peramivir 300 IV (N=384)	Peramivir 600 IV (N=386)	Oseltamivir 75 BID (N=365)
Any SAE	5 (1)	1 (<1)	2 (1)
Study 0815T0631			
Asthma	1 (<1)	0	0
Influenza	1 (<1)	0	0
Myalgia	1 (<1)	0	0
Pneumonia	1 (<1)	0	0
Vomiting	0	0	1 (<1)
Pneumonia bacterial	0	0	1 (<1)
Study 0816T0632			
Pneumonia	0	1 (<1)	
Pneumonia bacterial	1 (<1)	0	

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

Based on the three Shionogi trials of IV peramivir in acute uncomplicated influenza (Studies 0722T0621, 0815T0631, and 0816T0632), the incidence of SAEs were 1% (5/483) among subjects treated with 300 mg IV peramivir and 0.2% (1/483) among subjects treated with 600 mg IV peramivir.

7.3.3 Dropouts and/or Discontinuations

This section highlights the TEAEs associated with dropouts and/or discontinuations in the Phase 2/3 trials of adult subjects with acute uncomplicated influenza.

As study drug in these trials was administered as a single dose, no subject randomized to peramivir treatment discontinued dosing as a result of a TEAE. Twenty peramivir-treated subjects (1.4%), however, experienced a TEAE leading to study dropout. Of these, the most common TEAE was rash or drug eruption (3 subjects, 0.2%). No subjects in the placebo groups experienced a TEAE leading to study or study drug discontinuation. In the oseltamivir group, five subjects (1.4%) discontinued study drug due to a TEAE, vomiting being the most frequent cause (2 subjects, 0.5%).

In Phase 1 trials, one of 596 subjects (0.2%) treated with a single-dose of peramivir experienced a TEAE leading to discontinuation of study. This subject received ≥ 600 mg peramivir plus other active study drug and discontinued due to TEAE of 'viral gastroenteritis'.

Phase 2/3 Placebo-Controlled Trials in Acute Uncomplicated Influenza

Study 0722T0621

No subject discontinued study drug infusion in Study 0722T0621. No TEAEs consistent with infusion reaction, hypotension, syncope, or anaphylaxis were reported. One subject in the placebo group (Subject 187-4) withdrew from study on Day 8 due to a TEAE of worsening cough (Grade 2) that began on Day 6, but was not considered related to study drug by the investigator.

Studies BCX1812-211, -311, and -212

No subject discontinued study drug or withdrew from study due to a TEAE in Studies BXC1812-311 or -212. In Study BCX1812-211, the only subject withdrawn prematurely due to a TEAE was the aforementioned Subject 653-022, who was treated with 300 mg IM peramivir and was subsequently hospitalized with a clinical diagnosis of meningitis on Study Day (b) (6); this AE was serious and had a fatal outcome (see Section 7.3.1).

Phase 3 Non-Placebo Controlled Trials in Acute Uncomplicated Influenza

In Study 0816T0632 no subject discontinued study drug or withdrew from study due to a TEAE.

In Study 0815T0631, 28 subjects discontinued study drug or withdrew from study in relation to a TEAE, with similar rates (3%) across treatment groups (Table 23). By MedDRA SOC, TEAEs in the "Infections and Infestations" SOC were the most common AEs leading to discontinuation; their incidence was balanced between groups. Further intergroup comparisons were limited due to the overall low incidence of events. In general, however, AEs in the "Skin and Subcutaneous Tissue Disorders" SOC were more frequent among peramivir-treated subjects than in the oseltamivir group (4 subjects versus 0 subjects, respectively). In particular, three peramivir-treated subjects reported rash or drug eruption following administration of study drug, none of which was serious. On the other hand, gastrointestinal AEs leading to drug discontinuation, such as nausea, vomiting, or diarrhea, were reported only in the oseltamivir group.

This reviewer examined the CRF's for all subjects in Study 0815T0631who had "drug withdrawn" coded as the action taken for an AE and confirmed that all of the peramivir-treated subjects completed study drug dosing; thus, the AEs listed in Table 23 for the

peramivir groups represent AEs associated with study dropouts rather than study drug discontinuations.

Table 23: Adverse Events Leading to Study Drug Discontinuation or Dropouts - Study 0815T0631

Adverse Event leading to discontinuation	Number of Subjects (%)		
	Peramivir 300 mg IV (N=363)	Peramivir 600 IV (N=365)	Oseltamivir (N=365)
Any Adverse Event	9 (3)	10 (3)	9 (3)
Blood and lymphatic system disorders	1(<1)	0	0
Lymphadenopathy	1(<1)	0	0
Gastrointestinal disorders	2 (1)	1 (<1)	2 (1)
Abdominal pain upper	0	1 (<1)	0
Diarrhoea	0	0	1 (<1)
Gingival pain	1 (<1)	0	0
Nausea	0	0	1 (<1)
Salivary gland pain	1 (<1)	0	0
Vomiting	0	0	2 (1)
Infections and infestations	5 (1)	5 (1)	4 (1)
Acute sinusitis	1 (<1)	0	0
Bronchitis	1 (<1)	1 (<1)	1 (<1)
Bronchopneumonia	1 (<1)	0	0
Cystitis	0	1 (<1)	0
Herpes simplex	0	0	1 (<1)
Myringitis	0	1 (<1)	0
Nasopharyngitis	1 (<1)	1 (<1)	0
Pneumonia	1 (<1)	1 (<1)	1 (<1)
Pneumonia bacterial	0	0	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (<1)	1 (<1)
Arthralgia	0	1 (<1)	0
Back pain	0	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	0	0	2 (1)
Upper respiratory tract inflammation	0	0	2 (1)
Skin and subcutaneous tissue disorders	1 (<1)	3 (1)	0
Drug eruption	0	1 (<1)	0
Eczema	0	1 (<1)	0
Rash	1 (<1)	1 (<1)	0

Note: Subjects may have more than one adverse event listed
Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

7.3.4 Significant Adverse Events

This section highlights the significant AEs observed in the clinical trials of peramivir in adults with acute uncomplicated influenza. Significant AEs were defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of study drug, dose reduction, or significant additional concomitant therapy, other than those reported as serious. Severe adverse events, as per the DAIDS AE toxicity grading table, but not reaching regulatory definition of an SAE, were also included.

Phase 2/3 Placebo-Controlled Trials in Acute Uncomplicated Influenza

Study 0722T0621

Of the 298 subjects treated in Study 0722T0621, 268 subjects (90%) reported 761 nonserious TEAEs. The proportions of subjects with TEAEs were comparable across treatment groups: PRV 300 mg IV 88%, PRV 600 mg IV 90%, and placebo 91%. The vast majority of TEAEs were DAIDS Grade 1(mild).

Moderate (Grade 2) TEAEs were reported by a quarter of subjects overall, with higher proportions in the peramivir groups (PRV 300 IV 22%, PRV 600 IV 32%, placebo 19%). Most Grade 2 AEs were not considered related to study drug and nearly all were resolved or resolving at the end of follow-up. The only moderate AE that was not recovered and that was possibly related to study drug was a Grade 2 'blood bilirubin increased' TEAE in a subject treated with PRV 300 mg IV (Subject 160-2); the event was noted on Day 14 but still not recovered by Day 69.

Severe (Grade 3) TEAEs were reported in 10 subjects and are listed in Table 24. All severe AEs were in the "Investigations" SOC. The most frequently reported severe AE was QT prolongation, noted in three subjects in the placebo group and three subjects in the combined peramivir groups.

Table 24: Severe (DAIDS Grade 3) Nonserious Adverse Events - Study 0722T0621

Severe Adverse Event	Number of Subjects (%)		
	Peramivir 300 IV (N=99)	Peramivir 600 IV (N=99)	Placebo (N=100)
Any Severe AE	2 (2)	3 (3)	5 (5)
Blood creatinine increased	0	1 (1)	0
Blood glucose increased	0	1 (1)	1 (1)
Blood pressure increased	0	0	1 (1)
Electrocardiogram QT prolonged	2 (2)	1 (1)	3 (3)

Source: created by clinical reviewer using adverse events analysis dataset (ADAE.xpt) – Study 0722T0621

Of the ten Grade 3 TEAEs, only two were considered possibly related to study drug, both occurring in peramivir-treated subjects. Their cases are described here:

- **Subject 062-3** – *MedDRA PT* '*blood creatinine increased*' - This 37-year-old man was treated with peramivir IV 600 mg for influenza A/H3N2. He had mild diarrhea on presentation that lasted throughout the observation period. Acute renal dysfunction was noted on Day 3 with peak blood urea nitrogen (BUN) 17.7 mg/dL and serum creatinine 2.44 mg/dL (baseline 1.12 mg/dL). He had received loxoprofen sodium prior to treatment with peramivir and paracetamol on Days 1-3. Urine beta-N-acetyl-D-glucosaminidase (NAG) was elevated at 16.5 U/L (reference range: 0-10 U/L) on Day 3 and there was evidence of microalbuminuria. No action was taken for this event. His BUN remained constant and his serum creatinine normalized by Day 6; urinalysis was normal on Day 14.

- **Subject 157-1** – *MedDRA PT* '*electrocardiogram QT prolongation*' - This 32-year-old man was treated with peramivir IV 300 mg for influenza A/H3N2. He had numerous findings on Day 3 (Visit 2) including mild elevation in transaminases, proteinuria, and severe QTcF prolongation of 421.5 msec (baseline 360 msec). However, ECG was interpreted as normal at all visits. No action was taken for this event. His QTcF on Day 14 was 364.4 msec.

None of the TEAEs reported in Study 0722T0621, of any severity, required dose reduction, dose interruption, or concomitant medications. No TEAEs reported in this trial were consistent with infusion site reactions, anaphylactic reactions, hypotension, syncope, or near syncope.

Studies BCX1812-211, -311 and -212

Due to the low incidence of severe AEs within the individual trials of IM peramivir, data were pooled from across the three trials to better estimate AE incidence.

In contrast to Study 0722T062, only about a third of subjects (295/809 [37%]) treated in the three BioCryst trials reported a nonserious TEAE. The rates were similar across trials and treatment groups, except the peramivir 600 mg IM group had a smaller percentage overall (PRV 150 mg IM 38%, PRV 300 mg IM 41%, PRV 600 mg IM 28%, and placebo 39%). The vast majority of these events were mild or moderate and two-thirds were considered not related or unlikely related to study drug.

Overall, 17% of subjects had DAIDS Grade 2-4 nonserious TEAEs, with higher incidence in the placebo and PRV 300 mg IM groups (19%) compared with the PRV 150 mg and 600 mg IM groups (15% and 13%, respectively). Most Grade 2-4 nonserious TEAEs were reported under the "Gastrointestinal Disorders", "Nervous System Disorders", "Infections and Infestations", and "Investigations" SOCs. The most common Grade 2-4 nonserious TEAE was nausea, with the highest incidence in the PRV 300 mg IM group (6%). None of the TEAEs, regardless of severity, required study drug discontinuation, dose reduction or dose interruption.

In these IM trials, 16 subjects (2%) reported 18 nonserious TEAEs related to injection site reactions. No significant differences were noted in incidence by treatment group or peramivir dose level, except no subjects in the PRV 150 mg IM group reported such events. Most of the reports were consistent with injection site pain. Severity of these events was equally distributed between mild, moderate and severe, with no differences between treatment groups, although numerically the placebo group had more Grade 3 events than the peramivir groups (3 in the placebo group versus 1 each in the PRV 300 mg and 600 mg groups). In 8 of these cases, the AEs correlated with elevations in serum creatinine phosphokinase (CPK) levels, all of which were Grade 1 or 2 and all of which were improved or resolved by the end of study. Most of these injection site reactions were considered related to study drug, but did not require intervention; those that did were treated pharmacologically with analgesics. All injection site reactions resolved, except one: Subject 432-012 in BCX1812-212, who was treated with PRV 600 mg IM, reported Grade 2 bilateral gluteal soreness on Day 10 that was ongoing at end of follow-up; this subject's CPK level was 66 U/L at Screening, 604 U/L at Day 3 and 59 U/L and 64 U/L on Days 9 and 14, respectively..

Fifteen subjects (2%) also had TEAEs of 'syncope' or 'presyncope' that were identified by a customized query for "orthostatic hypotension". This was in contrast to Study 0722T062 where no such events were reported. Most of the events were vasovagal in nature, but were attributed to study drug nonetheless. Incidence rates were comparable across treatment groups, including the placebo group, except there were no such events in the PRV 300 mg IM group, arguing against a peramivir dose response. All of the events were mild or moderate and all resolved without sequelae; none required intervention or discontinuation, reduction, or interruption of study drug dosing. See Section 7.3.5 "Orthostatic Hypotension/Shock" for an integrated analysis of these types of events across all controlled trials of peramivir in acute uncomplicated influenza.

In addition, there was one report of a nonserious Grade 3 hypersensitivity event in one subject in Study BCX1812-211 and two reports of severe 'hot flush' in two subjects in BCX1812-212. The narrative for the subject with the severe hypersensitivity event is as follows:

- **Subject 006-019** – *MedDRA PT* '*hypersensitivity'* - This was 47-year-old woman treated with IM peramivir 300 mg in Study BCX1812-211. She developed a Grade 3 "allergic reaction to unknown substance" on Study Day 5 that was considered possibly related to study drug, but was not serious. The event was preceded by Grade 3 'urticaria' on Day 4. There was no change in her eosinophil count. The subject was treated with prednisone, diphenhydramine, and famotidine and the event was considered resolved by Day 14. This subject was subsequently determined not to have influenza infection.

The two cases of 'hot flush', one in the PRV 600 mg IM group and one in the placebo group, were both severe and both reported from the same U.S. site in Study BCX1812-212, beginning on Day 3. The verbatim term for each was "hot flashes". The case in the peramivir group was in a 40-year-old man with influenza A/H1N1, while the placebo

case was in a 36-year-old woman with influenza A/H1N1 (H275Y). Neither case was considered related to study drug and both resolved by Day 6 with no intervention. Please see Section 7.3.5 “Hypersensitivity Reactions” for discussion of other potential hypersensitivity reactions in the controlled trials of peramivir.

Overall, 34 subjects (4%) had 47 severe or life-threatening (Grade 3-4) nonserious TEAEs, of which 14 subjects (2%) had TEAEs that were considered possibly, probably, or definitely related to study drug (combined peramivir groups 6; placebo 8). No Grade 3-4 TEAE required discontinuation or change in study drug dosing. All but five of the 47 events resolved by the end of study; of the five that were unresolved (‘hyperglycaemia’, ‘headache’, ‘herpes simplex ophthalmic’, ‘sinusitis’, and ‘toothache’), three were in placebo group and two were in the PRV 600 mg IM group and none was considered related to study drug. The most common severe TEAE was ‘headache’, which occurred predominantly in the placebo group (1%), followed by ‘injection site pain’, which occurred as frequently in the placebo group (0.6%) as in the combined peramivir groups. Laboratory abnormalities were infrequently reported as severe AEs; by MedDRA PT, none of the AEs under the “Investigations” or “Blood and Lymphatic System Disorders” SOCs was reported in more than one subject.

Life-threatening (Grade 4) nonserious TEAEs were limited to two subjects in the placebo group of Study BCX1812-211 (‘neutropenia’ and ‘hyperglycaemia’). Neither event was considered related to study drug.

Table 25 summarizes the severe (Grade 3) nonserious TEAEs observed in the peramivir treatment groups, by MedDRA SOC and Preferred Term.

Table 25: Severe (DAIDS Grade 3) Nonserious Adverse Events in Peramivir-Treated Subjects - Studies BCX1812-211, -311, and -212

Severe Adverse Event	Number of Subjects (%)			
	Peramivir			Placebo (N=336)
	150 IM (N=108)	300 IM (N=165)	600 IM (N=200)	
Any Severe Adverse Event	4 (4)	6 (4)	4 (2)	20 (6)
General disorders and administration site conditions	0	2 (1)	1 (1)	3 (1)
Chest pain	0	1 (1)	0	0
Injection site pain/discomfort	0	1 (1)	1 (1)	3 (1)
Infections and infestations	1 (1)	0	1 (1)	4 (1)
Gastroenteritis	1 (1)	0	0	0
Herpes simplex ophthalmic	0	0	1 (1)	0
Gastrointestinal disorders	0	0	2 (1)	3 (1)
Diarrhoea	0	0	1 (1)	1 (<1)
Toothache	0	0	1 (1)	0

Nervous system disorders	1 (1)	0	0	4 (1)
Headache	1 (1)	0	0	3 (1)
Investigations	1 (1)	1 (1)	0	1 (<1)
Blood glucose increased	1 (1)	0	0	0
Neutrophil count abnormal	0	1 (1)	0	0
Musculoskeletal and connective tissue disorders	0	2 (1)	0	2 (1)
Musculoskeletal pain	0	1 (1)	0	0
Myalgia	0	1 (1)	0	0
Pain in extremity	0	1 (1)	0	1 (<1)
Skin and subcutaneous tissue disorders	0	1 (1)	0	2 (1)
Urticaria	0	1 (1)	0	0
Blood and lymphatic system disorders	1 (1)	0	0	1 (<1)
Neutropenia	1 (1)	0	0	1 (<1)
Vascular disorders	0	0	1 (1)	1 (<1)
Hot flush	0	0	1 (1)	1 (<1)
Immune system disorders	0	1 (1)	0	0
Hypersensitivity	0	1 (1)	0	0

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Analysis of Safety (ISS)

Non-Placebo Controlled Trials in Acute Uncomplicated Influenza

In Studies 0815T0631 and 0816T032, 552 of 1,135 treated subjects (46%) had 931 nonserious TEAEs. The vast majority of these TEAEs were mild or moderate and two-thirds were considered not related to study drug by investigators. A total of 73 subjects (6%) had severe events: 70 in Study 0815T0631 and three in Study 0816T0632. When data from these two trials were pooled, the incidence of severe nonserious AEs was comparable across treatment groups. In these Shionogi trials, all severe TEAEs were in the "Investigations" or "Blood and Lymphatic System Disorders" SOCs. The most frequently reported Grade 3 TEAEs by MedDRA PT were 'electrocardiogram QT prolonged' and 'neutrophil count decrease', with no major differences noted between the peramivir and oseltamivir treatment groups.

All severe AEs related to QTc prolongation were reported in Study 0815T0631 (and 0722T0621 - see Table 24). In the Shionogi trials, change in QTc was reported as an AE if there was a prolongation change from pre-dose value by ≥ 60 msec, or if the measured value was 480 msec or above. Such AEs were reported in 23 subjects in Study 0815T0631: 5 subjects (1%) in the PRV 300 mg group, 8 subjects (2%) in the PRV 600 mg group, and 10 subjects (3%) in the oseltamivir group. All ECGs were submitted to a central measurement facility and data were reviewed by an ECG interpretation advisor. Abnormal ECG interpretations were reported for only three of

these subjects (1 in each treatment group); the subject in the PRV 600 mg group (Subject 011.JBH07) had abnormal EGG at baseline. In all but one subject, the QTc prolongation events were not considered related to study drug by the investigators; the case of Subject 122.TAR01 in the PRV 600 mg group, which was considered possibly related, is discussed in Section 7.4.4. Moreover, review of the ECG data from this trial suggested that QTc prolongation occurred in all treatment groups and may have been an artifact caused by high mean baseline heart rates (likely due to fever and influenza illness) which could not be corrected for sufficiently and which may have resulted in a shortened range of mean baseline QTcF values.

Severe nonserious TEAEs occurring in 2 or more subjects in any treatment arm are summarized in Table 26. Clinically similar and relevant events were pooled to provide a more clinically relevant analysis of the safety data; the pooling for this analysis is detailed in the table footnotes.

Table 26: Severe Nonserious Adverse Events (DAIDS Grade 3) - Studies 0815T0631 and 0816T0632

Severe Adverse Event	Number of Subjects (%)		
	Peramivir 300 IV (N=384)	Peramivir 600 IV (N=386)	Oseltamivir (N=365)
Any Severe Adverse Event	19 (5)	31 (8)	23 (6)
Electrocardiogram QT prolonged	5 (1)	8 (2)	10 (3)
Neutrophil count decreased	3 (1)	9 (2)	7 (2)
Neutropenia	1 (<1)	0	2 (1)
Lymphocyte count decreased	1 (<1)	2 (1)	1 (<1)
Blood glucose increased	4 (1)	2 (1)	1 (<1)
Glucose urine present	2 (1)	3 (1)	1 (<1)
Blood phosphorus decreased	2 (1)	2 (1)	0
Blood urine present	1 (<1)	1 (<1)	0
Hemoglobin decreased	1 (<1)	1 (<1)	0
Blood pressure increased [a]	0	2 (1)	0
Urine ketone body present	0	1 (<1)	1 (<1)
Transaminase increased [b]	1 (<1)	1 (<1)	0

[a] Also includes MedDRA Preferred Term '*blood pressure systolic increased*' from the "*Blood and Lymphatic System Disorders*" System Organ Class.
[b] Combines MedDRA Preferred Terms '*alanine aminotransferase increased*' and '*gamma-glutamyltransferase increased*'
Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Analysis of Safety (ISS)

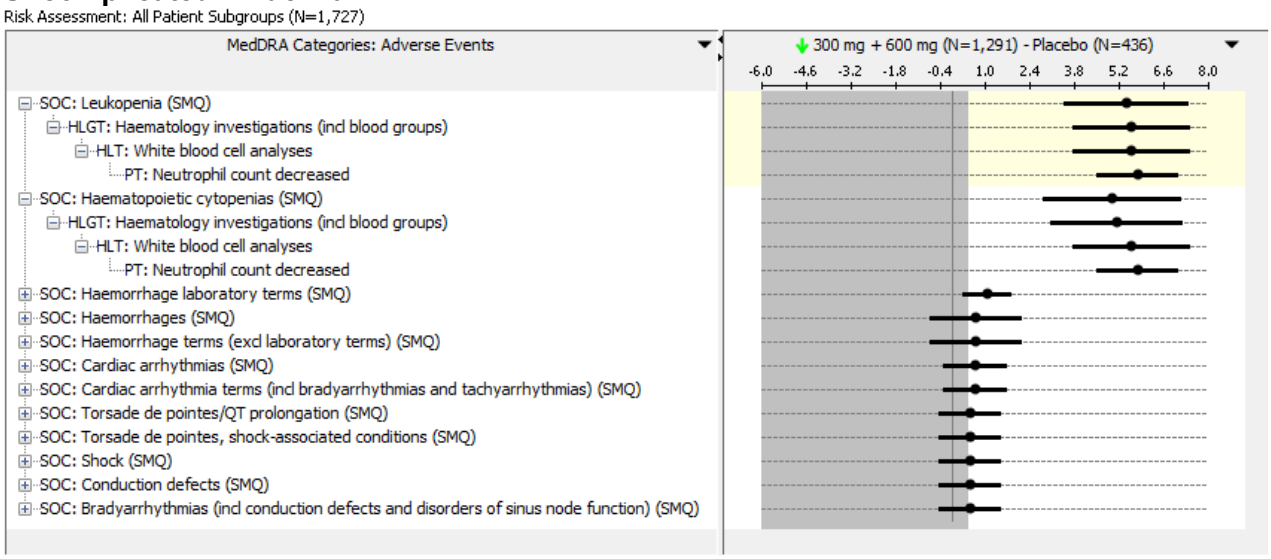
7.3.5 Submission Specific Primary Safety Concerns

Particular attention was paid to certain adverse events during the development of peramivir. Many of these were chosen as events of special interest because they had been observed with other NAIs and were noted in Warnings and Precautions of oseltamivir and zanamivir labeling. In particular, neuropsychiatric events, rash, hypersensitivity, liver enzyme abnormalities, and hemorrhagic colitis were events noted in the safety information of other NAIs. Renal toxicity was specified as an event of special interest for peramivir due to the nonclinical toxicity findings noted in rabbits (see Section 4.3). Other events were selected based on particular TEAE patterns noted in clinical trials of peramivir and other NAIs, including leukopenia, neutropenia, infusion site reactions, and muscle injury, or in the postmarketing setting, such as orthostatic hypotension/shock and convulsion.

Prespecified Standard MedDRA Queries (SMQ) version 12.1 and selected Preferred Terms were used to identify events of special interest in adults administered peramivir 300 mg or 600 mg (N=1,291) in the five controlled trials of acute uncomplicated influenza (total N=2,092).

As shown in Figure 6, when a risk assessment was performed for the combined peramivir groups (300 mg plus 600 mg) versus placebo, the only SMQs (narrow) that exhibited a ≥ 2% risk difference between peramivir and placebo were the Leukopenia and Haematopoietic Cytopenias SMQs. In both cases, the differences were driven by the MedDRA Preferred Term ‘neutrophil count decreased’. No significant differences were noted between peramivir doses in this or any other risk assessment conducted by this reviewer.

Figure 6: Adverse Events by Narrow MedDRA SMQ, Risk Difference ≥ 0.5% Total Peramivir (300 mg and 600 mg) versus Placebo - Controlled Trials in Acute Uncomplicated Influenza



Source: Created by clinical reviewer using MAED-generated SMQ datasets and JReview (datasets ADSL.xpt, ADAE.xpt), filter: TRTEMFL, NARROWSE

1) *Leukopenia and Neutropenia*

During the clinical development of peramivir, neutropenia and leukopenia were frequently reported AEs in both the Shionogi and BioCryst trials. Leukopenia and neutropenia were also included as clinically significant adverse reactions in the RAPIACTA package insert in Japan.

Narrow terms in the Leukopenia SMQ (MedDRA version 12.1) were used to analyze leukopenia and neutropenia adverse events of interest in the five controlled trials of acute uncomplicated influenza. By this method, 141 subjects were identified with suspected events. The broad SMQ search yielded six additional subjects, but five of these had lymphocyte or neutrophil '*percentage decreased*' as their event and were excluded from this analysis; another subject (Subject BCX1812-211.037.003, treated with peramivir 300 mg IM) had 'neutrophil count abnormal' reported as a TEAE, which was missed by the narrow SMQ search. Review of this subject's laboratory data revealed Grade 3 neutropenia and Grade 2 leukopenia on Day 3. As such, this subject was included in the subject counts for the peramivir 300 mg group.

Table 27 summarizes the leukopenia/neutropenia events of interest by MedDRA PT and treatment group; rates in the oseltamivir group are provided for comparison. None of these events was serious.

Table 27: Leukopenia Narrow SMQ Adverse Events (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

	Number of Subjects (%)			
Leukopenia SMQ (narrow)	**Peramivir 300 mg (N=627)**	**Peramivir 600 mg (N=664)**	**Placebo (N=436)**	**Oseltamivir (N=365)**
Any Leukopenia or Neutropenia Adverse Event	51 (8)	47 (7)	9 (2)	35 (10)
Neutrophil count decreased	37 (6)	38 (6)	0	32 (9)
White blood cell count decreased	12 (2)	13 (2)	7 (2)	2 (0.5)
Lymphocyte count decreased	1 (0.2)	2 (0.3)	0	1 (0.3)
Neutropenia	3 (0.5)	1 (0.2)	2 (0.5)	2 (0.5)
Neutrophil count abnormal [a]	1 (0.2)	0	0	0

a) 'Neutrophil count abnormal' added from broad SMQ search
Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

Of note, the majority of subjects with 'neutrophil count decreased' or 'neutropenia' reported as a TEAE were in the Shionogi trials, particularly Study 0815T0631, where nearly 10% of all peramivir-treated subjects had such events reported (compared with 9% in the oseltamivir group). In contrast, across all treatment groups in the three BioCryst trials, only 1 subject (0.1%) had 'neutrophil count decreased' reported as a TEAE (this subject was treated with peramivir 300 mg IM); four subjects (0.5%) had a TEAE of 'neutropenia' (PRV 150 mg 1, PRV 300 mg 1, placebo 2); and, as previously noted, one subject (0.1%) had 'neutrophil count abnormal'. When the safety analysis was limited to just the four placebo-controlled trials, the incidence of 'neutrophil count decreased' and 'neutropenia' in the combined peramivir 300 mg and 600 mg groups was only 0.2% for each term. Similarly, the risk difference (per hundred) for the narrow Leukopenia SMQ overall was only 0.96% for the combined 300 mg and 600 mg peramivir groups versus placebo when only the placebo-controlled trials were included, whereas it was 5.45% when Study 0815T0631 was included. The reasons for these disparities in AE reporting between the Shionogi and BioCryst trials are not clear, but they raise concerns about the reliability of pooled safety data from these different trials. 'Neutrophil count decreased' was also the most frequent abnormal laboratory AE reported in the Japanese pediatric trial of peramivir, Study 0918T0633 (reported in 25 subjects [21.4%]).

With respect to objective laboratory data, Table 28 displays the proportion of subjects in each treatment group who experienced treatment-emergent graded laboratory toxicities in leukocyte or neutrophil counts; the denominator within each group is the number of subjects with available baseline values. Again, no difference was noted between the 300 mg and 600 mg peramivir dose levels; however, a difference was detected between peramivir and placebo. Again, the difference was driven predominantly by subjects from

Study 0815T0631. When peramivir rates were compared with those of oseltamivir, however, no significant differences were noted, suggesting these laboratory toxicities may have been particular to the subject population or influenza season of Study 0815T0631. When data from Study 0815T0631 were excluded, the differences between the peramivir groups and placebo for either laboratory parameter were less apparent.

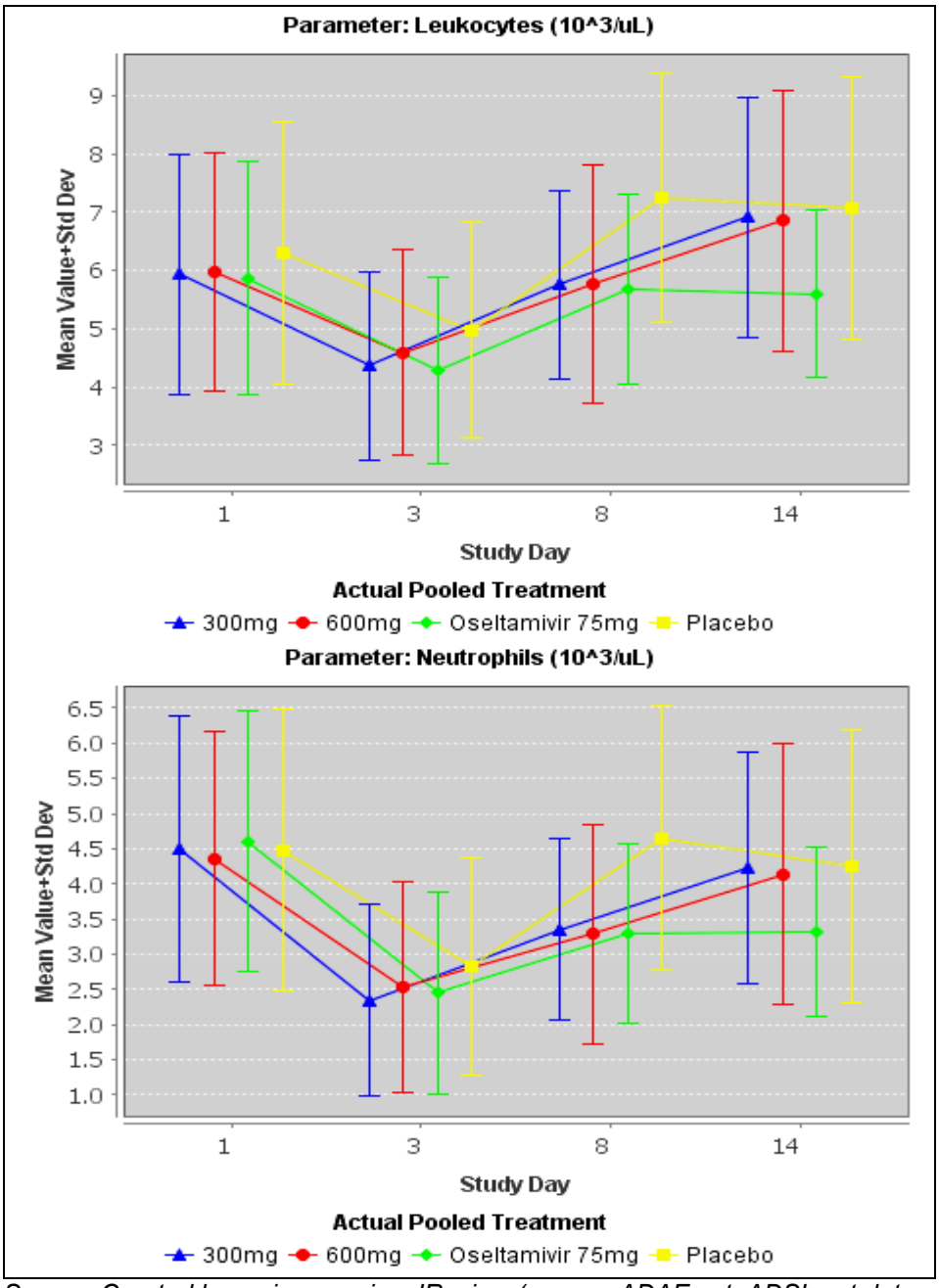
Table 28: Treatment-Emergent Leukocyte and Neutrophil Laboratory Abnormalities by Maximum Toxicity Grade (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Maximum Toxicity Grade	Peramivir 300 mg	Peramivir 600 mg	Placebo	Oseltamivir
Leukocytes (10^3/µL)	**N=617**	**N=657**	**N=430**	**N=362**
Any Grade	39 (6)	44 (7)	9 (2)	25 (7)
Grade 1 (2.0 - 2.5 x10^3/µL), n (%) Grade 2 (1.5 - 1.999 x10^3/µL), n (%)	34 (6) 5 (1)	38 (6) 6 (1)	9 (2) 0	23 (6) 2 (1)
Neutrophils (10^3/uL)	**N=617**	**N=654**	**N=425**	**N=362**
Any Grade	125 (20)	132 (20)	47 (11)	75 (21)
Grade 1 (1.0 - 1.3 x10^3/µL), n (%) Grade 2 (0.75 - 0.999 x10^3/µL), n (%) Grade 3 (0.50 - 0.749 x10^3/µL), n (%) Grade 4 (< 0.50 x10^3/µL), n (%)	70 (11) 45 (8) 7 (1) 3 (0.5)	78 (12) 42 (6) 9 (1) 3 (0.5)	20 (5) 16 (4) 10 (2) 1 (0.2)	41 (11) 25 (7) 7 (2) 2 (1)

N = number of subjects with baseline laboratory value
Source: created by clinical reviewer using laboratory analysis dataset (ADLB.xpt) – Integrated Summary of Safety (ISS)

Among the 387 subjects with treatment-emergent leukopenia or neutropenia laboratory toxicities, mean time to onset was 3 days (or the first follow-up visit). This was consistent across all treatment groups. Mean values by study day are shown in Figure 7. The vast majority of subjects normalized their laboratory values by end of study; only 10 subjects had abnormal values representing ≥ 1 toxicity grade shift from baseline at Day 14 or later, with comparable numbers in the peramivir and placebo groups (PRV 300 mg 2; PRV 600 mg 3; placebo 5).

Figure 7: Mean Leukocyte and Neutrophil Laboratory Values (x10^3/uL) by Study Day (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

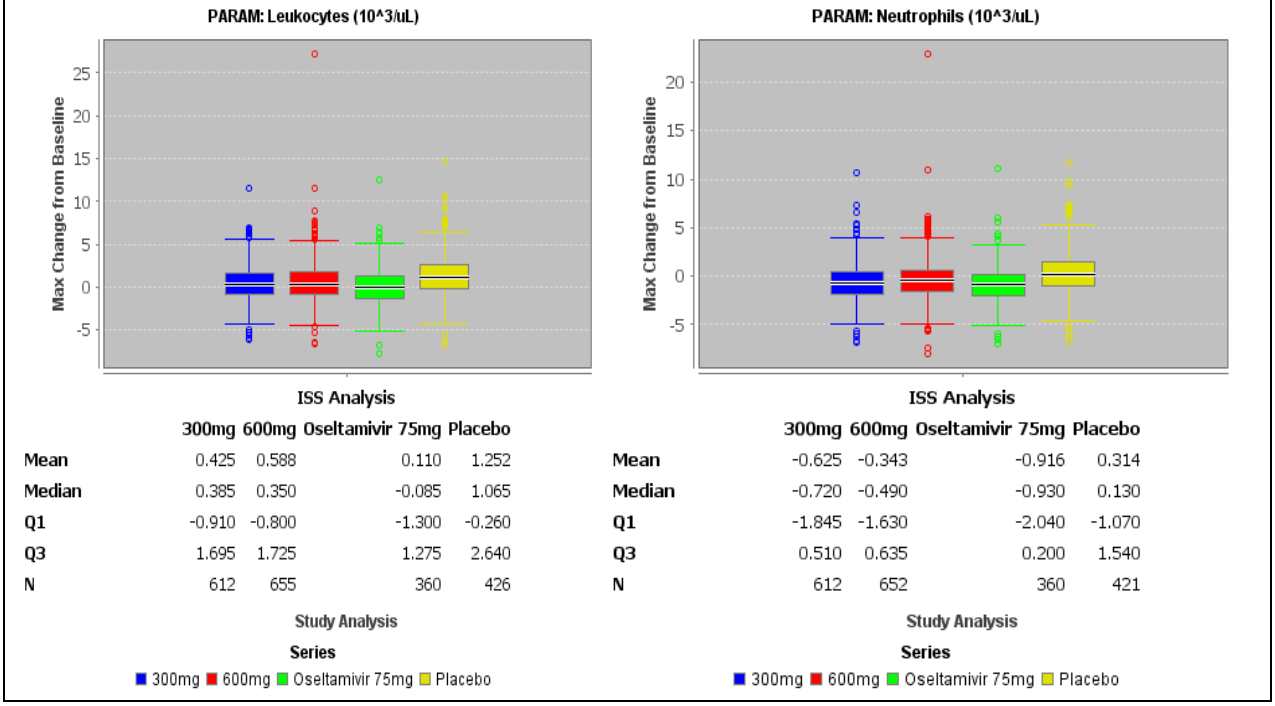


Source: Created by reviewer using JReview (source: ADAE.xpt, ADSL xpt datasets)

Maximum change from baseline leukocyte or neutrophil count by treatment group is displayed in Figure 8. Again, no dose response was detected between the two peramivir groups. While a difference was noted between peramivir and placebo, no such difference was noted when the comparison was made with oseltamivir. Moreover, no

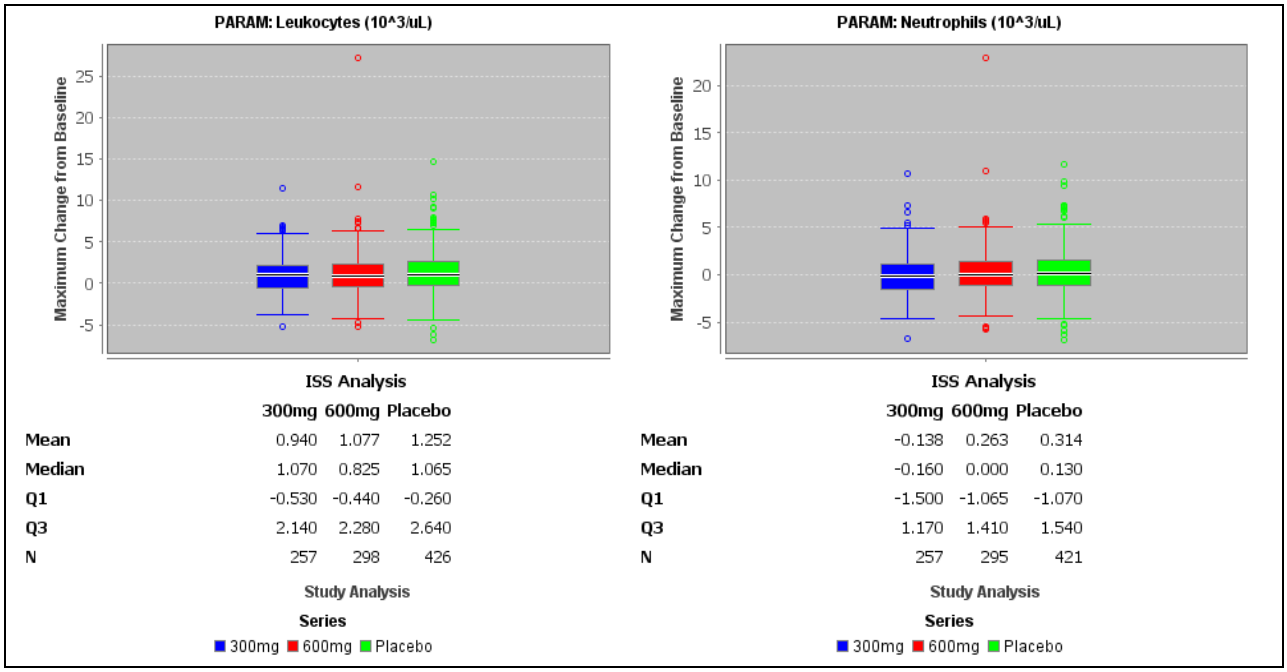
appreciable difference was noted between peramivir and placebo when the analysis excluded Study 0815T0631 (Figure 9).

Figure 8: Maximum Change from Baseline in Leukocyte and Neutrophil Counts (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza



Source: Created by reviewer using JReview (source: ADAE.xpt, ADSL xpt datasets)

Figure 9: Maximum Change from Baseline in Leukocyte and Neutrophil Counts (Peramivir 300 mg and 600 mg) - Placebo-Controlled Trials in Acute Uncomplicated Influenza



Source: Created by reviewer using JReview (source: ADAE.xpt, ADSL xpt datasets)

In summary, the clinical data from the five controlled trials in acute uncomplicated influenza suggest there might be a slight increase in the incidence of TEAEs and laboratory toxicities related to leukopenia and neutropenia with peramivir use compared with placebo. These events were generally self-limiting and not serious. Furthermore, the difference from placebo was substantially diminished when the non-placebo controlled Study 0815T0631 was excluded from the analyses. In that particular trial, the incidence of leukopenia/neutropenia TEAEs and laboratory toxicities in the peramivir groups was similar to that of the oseltamivir group. The totality of the data, therefore, does not support an increased risk of leukopenia or neutropenia associated with peramivir administration in adults with acute uncomplicated influenza.

The Applicant also reviewed the Japanese postmarketing data of peramivir using narrow terms in the Hematopoietic Leukopenia SMQ (MedDRA v16.0) and identified six adult patients with leukopenia/neutropenia events, four of which were serious. The serious events were review and all were found to be consistent with post-infection leukopenia and neutropenia. In addition, several patients had severe infections, particularly underlying influenza or sepsis, which provided a more reasonable etiology for the events. In summary, there was no compelling evidence that use of peramivir resulted in decreased leukocytes or neutrophils in the postmarketing setting.

2) *Hepatic Effects*

Based on several reports of hepatic dysfunction, FDA requested an integrated assessment of all hepatic function disorders from clinical trials and postmarketing during the development of peramivir. A report "Events of Hepatic Function Disorder" was submitted to IND 69,038 on May 27, 2011. This analysis reviewed all potential sources of information and focused on a range of potential drug-induced liver injuries. In brief, the analysis did not find an association between peramivir and hepatoxicity events. However, because of continued postmarketing reports of liver transaminase elevations and the importance of drug-induced liver injury (DILI), drug-induced hepatotoxicity remained an event of interest. Also, as noted in Section 2.6, hepatic dysfunction and jaundice were added in July 2013 to both the precautions and clinically significant adverse drug reactions section of the RAPIACTA (IV peramivir) package insert in Japan. This was based on an analysis of 8 of 15 SAEs reported in postmarketing for which a role of peramivir could not be excluded. Wording in the RAPIACTA label under clinically significant adverse drug reactions states:

> *"Hepatic dysfunction, jaundice (unknown incidence): Since hepatic dysfunction or jaundice accompanied by markedly increased AST (GOT), ALT (GPT), γ-GTP, ALP, etc. may occur in the early period such as the day following administration, patients should be carefully observed. If any abnormality is observed, administration should be discontinued and appropriate measures taken."*

For the FDA analysis of hepatotoxicity, the following narrow SMQs (MedDRA v12.1) were used: Hepatic Disorders; Liver Related Investigations, Signs and Symptoms; Drug Related Hepatic Disorders – Comprehensive Search; Hepatic Failure; Fibrosis and Cirrhosis and Other Liver Damage-Related Conditions; Hepatitis, Non-Infectious; and Cholestasis and Jaundice of Hepatic Origin. In addition, the following narrow SMQs were reviewed: Biliary Disorders; Biliary System Related Investigations, Signs, and Symptoms; and Functional, Inflammatory and Gallstone Related Biliary Disorders. Lastly, laboratory data were analyzed using Hy's Law criteria.

In the pooled analysis, 90 subjects were identified with hepatic or biliary events by narrow SMQ search, with similar percentages across treatment groups. Risk differences (per hundred subjects) for hepatic SMQ events were 0.6% and 0.4% versus placebo for the 300 mg and 600 mg peramivir groups, respectively. For the biliary SMQs, the risk differences were less than zero for any peramivir group versus placebo. (A broad SMQ search yielded only nonspecific cases, mostly of hypoalbuminemia and elevated alkaline phosphatase).

Table 29 displays the hepatic and biliary TEAEs identified by narrow SMQ analysis, by MedDRA HLT and Preferred Term. None of these events was serious. For each term, regardless of MedDRA hierarchy, the risk difference between the peramivir and placebo

groups was less than 1%, suggesting no major difference. There was, however, an imbalance with respect to severity whereby the proportion of subjects with moderate or severe (Grade ≥ 2) events was 53% and 42% in the peramivir 300 mg and 600 mg groups, respectively, compared with 18% in the placebo group.

Table 29: Hepatic and Biliary Narrow SMQ Adverse Events (Peramivir 300 mg and 600 mg) - Controlled Clinical Trials in Acute Uncomplicated Influenza

Hepatic and Biliary SMQs (narrow)	Number of Subjects (%)		
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=436)
Any Hepatoxicity Adverse Event	32 (5)	36 (5)	22 (5)
HLT Hepatic enzymes and function abnormalities	1 (0.2)	0	0
Hepatic function abnormal	1 (0.2)	0	0
HLT Liver function analyses	31(5)	36 (5)	22 (5)
Alanine aminotransferase increased	17 (3)	18 (3)	13 (3)
Aspartate aminotransferase increased	7 (1)	16 (2)	11 (3)
Bilirubin conjugated increased	1 (0.1)	1 (0.2)	1 (0.2)
Blood bilirubin increased	8 (1)	9 (1)	7 (2)
Gamma-glutamyltransferase increased	2 (0.3)	5 (1)	0
Hepatic enzyme abnormal	0	2 (0.3)	0
Hepatic enzyme increased	1 (0.2)	0	0
Liver function test abnormal	0	1 (0.2)	0
Urobilin urine present	2 (0.3)	0	2 (0.5)

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

By MedDRA PT, the 600 mg group had a slightly greater incidence of 'aspartate aminotransferase increased' than the 300 mg group, but the difference was small (2.4% versus 1.1%, respectively). Otherwise, no major differences were noted between the two peramivir doses with respect to incidence or severity of hepatic or biliary events.

Treatment-emergent graded laboratory toxicities in liver transaminases, alkaline phosphatase and total bilirubin levels are summarized in Table 30 by treatment group. In general, these laboratory toxicities represented a 1-grade shift from baseline. The PRV 600 mg group had a greater incidence of treatment-emergent Grade 1 and 2 elevated aspartate aminotransferase (AST) and Grade 2 elevated alanine aminotransferase (ALT) than either the PRV 300 mg or placebo group.

Table 30: Treatment-Emergent Graded Liver-Related Laboratory Abnormalities by Maximum Toxicity Grade (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Maximum Toxicity Grade	Peramivir 300 mg	Peramivir 600 mg	Placebo
Alanine Aminotransferase (U/L)	**N=618**	**N=654**	**N=430**
Any Grade	46 (7)	58 (9)	39 (9)
Grade 1 (1.25 - 2.5 x ULN), n (%) Grade 2 (2.6 - 5.0 x ULN), n (%) Grade 3 (5.1 - 10.0 x ULN), n (%) Grade 4 (>10.0 x ULN), n (%)	36 (6) 10 (2) 0 0	38 (6) 19 (3) 1 (0.2) 0	31 (7) 5 (1) 1 (0.2) 2 (0.5)
Aspartate Aminotransferase (U/L)	**N=610**	**N=644**	**N=428**
Any Grade	59 (10)	97 (15)	46 (11)
Grade 1 (1.25 - 2.5 x ULN), n (%) Grade 2 (2.6 - 5.0 x ULN), n (%) Grade 3 (5.1 - 10.0 x ULN), n (%)	50 (8) 9 (2) 0	83 (13) 13 (2) 1 (0.2)	36 (8) 7 (2) 3 (1)
Alkaline Phosphatase (U/L)	**N=623**	**N=657**	**N=434**
Any Grade	0	5 (1)	5 (1)
Grade 1 (1.25 - 2.5 x ULN), n (%)	0	5 (1)	5 (1)
Bilirubin (mg/dL)	**N=624**	**N=660**	**N=433**
Any Grade	12 (2)	15 (2)	10 (2)
Grade 1 (1.1 - 1.5 x ULN), n (%) Grade 2 (1.6 - 2.5 x ULN), n (%) Grade 3 (2.6 - 5.0 x ULN), n (%)	8 (1) 4 (1) 0	12 (2) 3 (0.5) 0	7 (2) 2 (2) 1 (0.2)

N = number of subjects with baseline laboratory values
Source: created by clinical reviewer using laboratory analysis dataset (ADLB.xpt) – Integrated Summary of Safety (ISS)

Among subjects with graded treatment-emergent elevations, median time to serum ALT elevation was 5 days for PRV 300 mg, 6 days for PRV 600 mg, and 8 days for placebo; median time to serum AST elevation was 3 days for all groups. Elevations in total bilirubin tended to occur later, with a median time to onset of 14-16 days; the placebo group had the shortest time to onset.

As part of the hepatoxicity assessment, this reviewer conducted two additional analyses of the laboratory data. First, subjects experiencing treatment-emergent ALT or AST ≥ 3x and ≥ 5x ULN without significant total bilirubin elevation i.e., total bilirubin < 2x ULN, were analyzed. Second, the laboratory criteria for Hy's Law (ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN with alkaline phosphatase < 2x ULN) were applied to the data.

By the first analysis, 30 subjects were identified with ALT or AST levels ≥ 3x ULN (with no significant increase in total bilirubin): PRV 300 mg 7 (1%); PRV 600 mg 16 (2%); and placebo 7 (2%). As noted previously, most liver enzyme elevations were reported by

Day 3. Sustained elevations were uncommon and most subjects who experienced transaminase elevations had resolving values by their next visit (typically Day 7 or 8). Two-thirds of these subjects normalized their values by end of follow-up (typically Day 14); those that did not (PRV 300 mg 3; PRV 600 mg 4; placebo 3) tended to have elevated transaminases at baseline or had other confounding issues, such as concomitant medication use.

Among these 30 subjects, seven had treatment-emergent ALT or AST levels that were ≥ 5x ULN; three were treated with peramivir (PRV 300 mg 1; PRV 600 mg 2) and four received placebo. The cases of three peramivir-treated subjects are summarized here based on the available clinical data:

- **Subject BCX1812-212.103.002** was a 42-year-old female in New Zealand, with no significant past medical history, treated with peramivir 600 mg IM for influenza B. Two TEAEs of 'liver function test abnormal' and 'nausea' were reported on Study Day 3. Both were mild and considered possibly related to study drug by the investigator. The nausea resolved by Day 6, but 'abnormal liver function test' was reported as lasting 55 days. The subject's baseline ALT was 77 U/L (Grade 1); baseline AST was not recorded. By Day 3 (first follow-up visit), serum ALT and AST were both Grade 3 (i.e., 250 U/L and 198 U/L, respectively). Serum bilirubin and alkaline phosphatase remained normal. No action was taken with respect to the elevated transaminases. Concomitant medications included paracetamol, benzydamine hydrochloride, cough syrup, and "other analgesics and antipyretics". By the next follow-up visit (Day 8), ALT and AST were decreased at 172 U/L (Grade 2) and 87 U/L (Grade 1), respectively. By Day 14, ALT levels had decreased further to Grade 1 and AST had normalized. The subject was seen again on Day 57, at which point both AST and ALT were within normal limits.

  Medical Officer's comment: In this case, assessment of DILI is confounded by concomitant medications (acetaminophen) and elevated transaminase levels at baseline, suggesting influenza illness as possible alternate etiology.

- **Subject BCX1812-212.303.018** was a 21-year-old male in South Africa, with no significant past medical history, treated with peramivir 600 mg IM for influenza A/H1N1 (H275Y). Baseline ALT and AST were 40 U/L and 143 U/L (Grade 2), respectively. His ALT and AST levels increased to 78 U/L (Grade 1) and 234 U/L (Grade 3) by Day 3. No TEAEs or concomitant medications were reported and no action was taken for the elevated transaminases. Both ALT and AST normalized by the next visit (Day 9); however, his serum bilirubin became slightly elevated at 1.3 mg/dL (baseline 0.6 mg/dL; ULN = 1.2 mg/dL). By Day 15, all three parameters were within normal limits.

  Medical Officer's comment: In this case, Grade 2 AST elevation at baseline suggests an alternate etiology, probably influenza illness.

- **Subject 0815T0631.137.TLU19** was 30-year-old male in Taiwan, with history of allergic rhinitis and hypersensitivity to several drugs (aspirin, non-steroidal anti-inflammatory agents) treated with peramivir 300 mg IV for influenza A/H1N1. Pre-treatment transaminase levels were not recorded (but baseline bilirubin was normal), nor were there any laboratory records

for Day 3. On Day 8, his serum ALT and AST were 229 U/L (Grade 3) and 67 U/L (Grade 1), respectively. Severe 'alanine aminotransferase increased' was reported as a TEAE on that day, but no action was taken. No concomitant medications were reported. His transaminase levels were normal by the next visit (Day 27) and the TEAE was reported as resolved.

Medical Officer's comment: Incomplete laboratory data in this case, including a lack of baseline ALT and AST values, precludes an adequate assessment of DILI.

In the second analysis, no subject in the adult clinical trials of acute uncomplicated influenza met Hy's Law criteria. Nor did any subjects in Phase 1 trials in healthy volunteers meet these criteria. There was one case in the hospitalized Study BCX1812-303 that met the first two criteria of Hy's Law (i.e., transaminase elevation ≥ 3x ULN and serum total bilirubin ≥ 2x ULN), but the case was highly confounded by underlying critical illness, cholelithiasis, and concomitant medication use.

In the Applicant's analysis of the postmarketing experience, 28 cases of possible drug-induced hepatotoxicity were identified, 17 of which were serious (15 in adults, 2 in pediatrics). All cases were heavily confounded and had numerous potential causes for hepatotoxicity. Many of the patients had significant comorbidities or severe influenza, and most were on concomitant medications with hepatotoxic potential. Some of the cases also appeared to have a cholestatic pattern, suggesting biliary system dysfunction.

In summary, while there is a suggestion of mild transaminitis with peramivir use based on the clinical trial laboratory data, there is no compelling evidence to suggest an increased risk of drug-induced liver injury.

3) *Muscle Effects*

Increases in serum CPK levels were among the most commonly reported TEAEs in IM peramivir trials. Increased serum CPK may be considered a marker for muscle penetration in the context of IM injections; in these trials, CPK levels returned to baseline level by Day 5 in most subjects.

Both the broad and narrow Rhabdomyolysis/Myopathy SMQ were used by the Applicant and this reviewer to identify potential cases of muscle injury. The narrow SMQ yielded only three cases, all from clinical trials in hospitalized subjects (Studies BCX1812-301 and -303) and none of which were considered related to study drug by the investigators.

By the broad SMQ search, 38 TEAEs in 37 subjects were identified in the five trials of acute uncomplicated influenza (PRV 300 mg 2%, PRV 600 mg 3%, and placebo 1%); an additional 2 subjects each were identified in the PRV 150 mg and oseltamivir groups. Risk differences (per hundred subjects) for the broad Rhabdomyolysis/Myopathy SMQ were 0.97% and 1.72% for PRV 300 mg and PRV 600 mg, respectively, versus placebo. The most common TEAE by MedDRA Preferred Term was 'blood creatinine

phosphokinase increased', for which the greatest difference was between the PRV 600 mg group and placebo (risk difference = 1.65%); however, CPK increases were seen across all treatment groups, including the oseltamivir group in Study 0815T0631, suggesting these events may have been related to influenza itself rather than treatment. Given the small number of events, no appreciable dose response was noted for peramivir; the relative risk ratio for the Rhabdomyolysis/Myopathy SMQ was 1.38 for PRV 600 mg versus PRV 300 mg.

The TEAEs are listed by MedDRA PT and summarized by treatment group in Table 31. About 60% (23/37) of these subjects were in the BioCryst trials of IM peramivir. None of the identified muscle injury events was serious. Most of the events were mild or moderate; severe events were limited to six events: CPK increase (PRV 300 mg 1), blood creatinine increased (PRV 600 mg 1), musculoskeletal pain or myalgia (PRV 300 mg 3), and myositis (placebo 1). Of note, myalgia was one of the possible seven influenza symptom used in the entry criteria for these trials.

Table 31: Rhabdomyolysis/Myopathy Broad SMQ Adverse Events (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Rhabdomyolysis/Myopathy SMQ (broad)	Number of Subjects (%)		
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=463)
Any Muscle Injury Adverse Event	13 (2)	19 (3)	5 (1)
Blood creatine phosphokinase increased	6 (1)	14 (2)	2 (0.5)
Myalgia	4 (1)	3 (0.5)	2 (0.5)
Myalgia intercostal	1 (0.2)	0	0
Musculoskeletal pain	1 (0.2)	0	0
Myositis	0	0	1 (0.2)
Blood calcium decreased	1 (0.2)	0	0
Renal failure	0	1 (0.2)	0
Renal impairment	0	1 (0.2)	0
Blood creatinine increased	0	1 (0.2)	0

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

Graded treatment-emergent elevations in CPK were noted in 191 subjects, across all treatment groups; however, 93% of these subjects were in the BioCryst trials of IM peramivir. Conversely, very few oseltamivir-treated subjects experienced CPK level elevations (5 subjects [1.4%] – all Grade 1). The numbers of subjects with treatment-emergent CPK elevations are displayed in Table 32, by maximum toxicity grade and treatment group.

Table 32: Treatment-Emergent Creatinine Phosphokinase Elevations by Maximum Toxicity Grade (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Maximum Grade Toxicity	Peramivir 300 mg	Peramivir 600 mg	Placebo
Creatinine Phosphokinase (U/L)	**N=621**	**N=654**	**N=431**
Any Grade	44 (7)	96 (15)	35 (8)
Grade 1 (3.0 - 5.9 x ULN), n (%) Grade 2 (6.0 - 9.9 x ULN), n (%) Grade 3 (10.0 - 19.9 x ULN), n (%) Grade 4 (≥ 20.0 x ULN), n (%)	25 (4) 13 (2) 3 (0.5) 3 (0.5)	67 (10) 23 (4) 6 (1) 0	26 (6) 3 (1) 6 (1) 0

N = number of subjects with baseline laboratory values
Source: created by clinical reviewer using laboratory analysis dataset (ADLB.xpt) – Integrated Summary of Safety (ISS)

As shown in Table 32, the peramivir 600 mg group had a greater percentage of subjects with Grade 1 or 2 CPK elevations than either the peramivir 300 mg or placebo groups. However, Grade 3-4 CPK elevations were evenly distributed across treatment groups. When the analysis was limited to just the IV peramivir trials (0722T0621 and 0815T0631), the number of subjects with CPK elevations was much smaller (PRV 300 mg 4 [0.8%]; PRV 600 mg 4 [0.9%]; placebo 0; oseltamivir 5 [1.4%]) and no dose response was observed for peramivir. These findings serve to highlight the link between the IM route of administration and risk of CPK elevations.

In the Phase 1 program, CPK increases were seen in 5-9% of peramivir-treated subjects and occurred exclusively with IM administration. In the Shionogi postmarketing database, muscle injury events were reported in 7 adult patients and 1 pediatric patient. Among these were two SAEs of rhabdomyolysis in adults. All of the cases were confounded by underlying illness and comorbidities.

In summary, muscle injury events associated with peramivir were mostly mild to moderate and largely limited to the IM route of administration. There was little clinical evidence to suggest that IV peramivir was associated with muscle injury.

4) *Nephrotoxicity*

Based on nephrotoxicity observed in a single species (rabbits) in nonclinical studies (see Section 4.3), FDA requested that renal safety monitoring data be specifically collected and analyzed to evaluate the potential renal effects of peramivir in humans. Both narrow and broad terms in the Acute Renal Failure SMQ (MedDRA v12.1) were used to analyze renal events of interest in the five controlled trials in acute uncomplicated influenza.

By this method, 135 treatment-emergent renal events were identified in 132 subjects across all treatment groups (including oseltamivir). The most commonly reported TEAE was proteinuria, with comparable rates in each group (4-6%). No risk difference was noted between the peramivir and control groups. Renal events in the peramivir groups tended to be mild or moderate, whereas those in the placebo group were nearly always mild; severity of renal events in the oseltamivir group was comparable to that in the peramivir groups. There was also no notable difference between treatment groups in mean time to onset or duration of events; most renal events occurred between 3 and 5 days across groups. No significant dose effect was observed for peramivir with respect to incidence, type, or severity of renal TEAEs.

None of the identified renal events was serious and none required intervention, except in the case of one subject (Subject BCX1812-212.311.016) who received peramivir 600 mg IM on Day 1 and was treated with 2 liters IV fluids on Day 3 for Grade 2 'renal impairment' (serum creatinine = 4.8 mg/dL, Grade 4) that was not considered related to study drug. This subject had elevated serum creatinine at baseline (3.59 mg/dL, Grade 3) and also received a concomitant course of fluoroquinolones for presumptive pneumonia; serum creatinine began to normalize by Day 4 and was within normal limits on Days 9 and 14.

A single case of 'renal failure' was identified in a 22-year-old man in Study BCX1812-212 (Subject 428.007) treated with peramivir 600 mg IM. This subject had a serum creatinine of 1.35 mg/dL at baseline, with 2+ proteinuria. His serum creatinine gradually decreased over the subsequent week, but transiently increased to 1.4 mg/dL on Day 14. A TEAE of mild 'renal failure' was reported on that day (verbatim: "mild renal insufficiency"). Repeat testing a week later (Day 22) showed serum creatinine was 1.01 mg/dL. The proteinuria diminished to trace by Day 14 and was negative by Day 22.

When the laboratory data from these five trials were reviewed, few subjects were found to have treatment-emergent graded elevations in serum creatinine (Table 33). Most of the toxicities were Grade 1, but three subjects experienced Grade 3 or 4 elevations in serum creatinine (PRV 600 mg 2; oseltamivir 1). One of these was the aforementioned Subject BCX1812-212.311.016 (PRV 600 mg IM), who had Grade 3 elevated serum creatinine at baseline. The other peramivir-treated subject was in Study 0722T0621 (Subject AA1.062-3), treated with peramivir 600 mg IV, who experienced a transient Grade 3 increase in serum creatinine on Day 3 (peak 2.44 mg/dL; baseline 1.12 mg/dL). A TEAE of severe 'blood creatinine increase' was reported on that day. This subject's serum creatinine normalized by the next visit (Day 6) and remained normal through the end of follow-up (Day 14). The last subject (Subject 112.KLC07) received oseltamivir in Study 0815T0631; this subject also experienced transient Grade 3 elevation in serum creatinine on Day 3 (peak 2.5 mg/dL) that resolved by the next visit (Day 8).

Table 33: Treatment-Emergent Serum Creatinine, Urine Protein and Urine Erythrocyte Laboratory Abnormalities by Maximum Toxicity Grade (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Maximum Toxicity Grade	Peramivir 300 mg	Peramivir 600 mg	Placebo	Oseltamivir
Creatinine (mg/dL)	**N=627**	**N=664**	**N=434**	**N=364**
Any Grade	2 (0.3)	4 (1)	2 (0.5)	1 (0.3)
Grade 1 (1.1 - 1.3 x ULN), n (%) Grade 3 (1.9 - 3.4 x ULN), n (%) Grade 4 (≥ 3.5 x ULN), n (%)	2 (0.3) 0 0	2 (0.3) 1 (0.2) 1 (0.2)	2 (0.5) 0 0	0 1 (0.3) 0
Urine Protein	**N=622**	**N=660**	**N=435**	**N=365**
Any Grade	126 (20)	127 (19)	83 (19)	104 (29)
Grade 1 (1+), n (%) Grade 2 (2-3+), n (%) Grade 3 (4+), n (%)	98 (16) 28 (5) 0	100 (15) 26 (4) 1 (0.2)	61 (14) 22 (5) 0	79 (22) 25 (7) 0
Urine Erythrocytes (/HPF)	**N=588**	**N=538**	**N=298**	**N=365**
Any Grade	48 (8)	56 (10)	40 (13)	36 (10)
Grade 1 (6-10 RBC/HPF), n (%) Grade 2 (> 10 RBC/HPF), n (%)	10 (2) 38 (7)	16 (3) 40 (7)	11 (4) 29 (10)	6 (2) 30 (8)

N = number of subjects with baseline laboratory values
Source: created by clinical reviewer using laboratory analysis dataset (ADLB.xpt) – Integrated Summary of Safety (ISS)

As also shown in Table 33, treatment-emergent proteinuria was reported in approximately one-fifth of all subjects in the peramivir and placebo groups. In all treatment groups, the majority of urine protein abnormalities were mild and documented at a single visit (typically at Day 3). Eleven subjects (1.6%) in the PRV 600 mg group had proteinuria documented on more than one occasion, but seven of these subjects had trace or 1+ proteinuria at baseline.

Similarly, mild to moderate hematuria was seen across all treatment groups, with the highest incidence in the placebo group. Of the 180 subjects with documented hematuria, the majority (86%) had hematuria at a single visit, typically at Day 3. Twenty-four subjects had hematuria at more than one visit, 20 of whom had Grade 0 urine erythrocytes at baseline, but the proportions were comparable between treatment groups (PRV 300 mg 6 [1%], PRV 600 mg 5 [0.9%], placebo 7 [2.3%], oseltamivir 2 [0.5%]).

Pyuria is not a graded laboratory parameter in the DAIDS toxicity grading table. However, because 'white blood cells urine positive' was one of the most common TEAEs reported in these trials (see Table 39), this reviewer undertook a descriptive analysis of treatment-emergent pyuria using the urinalysis datasets from the five controlled trials. No difference was noted in the incidence of pyuria between the two

peramivir dose groups. Further, the incidence was less in the peramivir groups (6-7%) than in the placebo group (10%) and comparable to that of the oseltamivir group (6%).

In the Phase 1 program, two subjects (0.3%) in the single-dose trials and none in the multiple-dose trials experienced a renal TEAE. In both cases, the renal event was proteinuria. In postmarketing, seven cases of renal toxicity were reported in adults, and one in pediatrics (see Section 7.6.3 “Nephritis”). Most of the adult cases occurred in elderly patients with comorbidities and multiple concomitant drugs. None of the cases provided compelling evidence of a role for peramivir in renal failure.

In summary, the totality of the data does not indicate an association between peramivir and renal toxicity.

5) Rash

Severe rashes such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in the postmarketing experience with other NAIs. In addition, in the Shionogi postmarketing experience of RAPIACTA, there was one spontaneous SAE report of Stevens-Johnson syndrome in an adult. Further, there was one subject in Study BCX1812-303 who experienced the TEAE of mild, nonserious erythema multiforme. As such, rash was an event of special interest during the review of this application.

For the analysis of rash events, this reviewer first conducted a broad search using the MedDRA SOC “Skin and Subcutaneous Tissue Disorders” and the following selected MedDRA Preferred Terms:

- Blister
- Dermatitis
- Dermatitis atopic
- Drug eruption
- Erythema
- Periorbital oedema
- Pruritus
- Rash
- Rash papular
- Rash pruritic
- Rash vesicular
- Skin exfoliation
- Skin lesion
- Urticaria

By this analysis, 31 rash events/subjects were identified, representing all treatment groups (Table 34). The percentage of subjects with these TEAEs was slightly greater by in the peramivir groups (1.8% for the combined 300 mg and 600 mg groups) than in the comparator groups. However, no particular term, regardless of MedDRA hierarchy level, was noted at significantly higher incidence (i.e., ≥ 1% risk difference) in the peramivir groups than in the comparator groups. Again, no dose effect was noted for peramivir with respect to incidence, type or severity of these TEAEs. None of these events was serious and none prompted any action to be taken, other than pharmacological intervention for 1 case each of urticaria and pruritus. Mean time of onset was 3 days

across treatment groups. Mean duration of events was 7-8 days for the peramivir groups, 10 days in the oseltamivir group, and 5 days in the placebo group.

Table 34: Skin and Subcutaneous Tissue Disorders SOC Adverse Events (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Skin and Subcutaneous Tissue Disorders (SOC)	Number of Subjects (%)			
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=436)	Oseltamivir (N=365)
Any Rash Adverse Event	13 (2)	10 (2)	6 (1)	2 (0.5)
Rash	4 (1)	5 (1)	3 (1)	0
Rash papular	0	0	1 (0.2)	0
Rash pruritic	1 (0.2)	0	0	1 (0.3)
Rash vesicular	1 (0.2)	0	0	0
Drug eruption	0	1 (0.2)	0	0
Urticaria	2 (0.3)	2 (0.3)	0	0
Pruritus	2 (0.3)	0	0	0
Dermatitis	0	1 (0.2)	0	0
Skin exfoliation	0	1 (0.2)	0	0
Blister	1 (0.2)	0	0	0
Dermatitis atopic	1 (0.2)	0	0	0
Erythema	0	0	1 (0.2)	1 (0.3)
Periorbital oedema	0	0	1 (0.2)	0
Skin lesion	1 (0.2)	0	0	0

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

In the next analysis, the following narrow terms in the Severe Cutaneous Adverse Reactions SMQ (MedDRA v12.1) were used to analyze potentially severe rash events:

- Acute generalised exanthematous pustulosis
- Cutaneous vasculitis
- Dermatitis bullous
- Dermatitis exfoliative
- Dermatitis exfoliative generalised
- Epidermal necrosis
- Erythema multiforme
- Exfoliative rash
- Skin necrosis
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Toxic skin eruption

No subject in any of the clinical trials of acute uncomplicated influenza (adult or pediatric) was identified with any of these terms.

In the clinical trials of hospitalized subjects, one subject in Study BCX1812-303 (Subject 132.003) experienced an event of mild, nonserious 'erythema multiforme'. Her narrative is as follows:

> The subject was a 28-year-old woman with a history of herpes simplex infection who developed ARDS and sepsis and was intubated. The subject received 10 days of IV peramivir since the criteria for clinical resolution on Study Day 5 were not met. No diagnosis of influenza was confirmed despite rapid antigen test, nasopharyngeal PCR test and culture. The event of mild 'erythema multiforme' appeared on Study Day 11. Although the investigator believed the event could be possibly related to peramivir, the subject had numerous other risk factors, including critical infection, history of herpes simplex virus, and polypharmacy.

No other events of severe cutaneous AEs were observed in the clinical development program of peramivir.

In postmarketing, there have been three reports of serious skin rash events, including one of Stevens-Johnson syndrome and two of exfoliative dermatitis. These are described here:

- *Stevens-Johnson Syndrome*
  - A 68-year-old man developed delirium and a rash on his face and body with oral lesions and bulbar conjunctival erythema (b) (6) days after he received peramivir for influenza and while he was on laninamivir for continued antiviral treatment. He left the hospital against medical advice but returned for outpatient care with systemic steroids and recovered.

- *Exfoliative Dermatitis*
  - A 30-year-old woman with a history of drug hypersensitivity received 1 dose of peramivir for influenza. Within 3 to 4 hours, she developed skin redness and itching over her entire body. She was seen the following day and was started on a 3-day outpatient treatment of IV steroids with good resolution of her itching. Later, she developed purpura over a portion of her body. Although the physician reported the event as erythroderma, he also indicated that there was no exfoliation, making the diagnosis uncertain. The etiology of the purpura was unclear. The reporter indicated that the patient was not on any other medications at the time of the event.
  - A 12-year old boy developed fever and received peramivir for suspected influenza. He also received fosfomycin, cefdinir, ambroxol, and a combination cold remedy concomitantly. The next day, he developed a rash on his face, ears, and chest with bulbar conjunctival erythema. There were no mucosal lesions. The rash subsequently desquamated. (b) (6) week after receiving peramivir, he continued to have malaise and poor appetite. The rash was more diffuse, and he

> was admitted to the hospital. No medical treatment for the rash was given, and he gradually improved.

Although these patients often had confounding factors, it is possible that peramivir played a role in these significant rash events.

In conclusion, while rash events were seen with peramivir in the clinical trials of acute uncomplicated influenza, they generally did not occur at a rate significantly greater than placebo and they tended to be mild, non-serious and self-limiting. Nevertheless, severe cutaneous AEs were reported with peramivir use in other trial settings and in postmarketing. Therefore, consistent with labeling for other NAI drugs, a Warning and Precaution regarding the risk of serious skin reactions is recommended.

6) Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported in the postmarketing setting for other NAIs, and anaphylaxis is cited in the Warnings and Precautions for other NAIs. In addition, there have been postmarketing reports from Japan that have used the term 'anaphylaxis' in association with peramivir treatment. The Applicant's analysis of these events, however, concluded that none of them met established criteria for anaphylaxis; all events with complete details were consistent with vasovagal events and recovered rapidly with minimal to no intervention other than placing the subject in a supine recumbent position.

Using the narrow terms of the Anaphylactic Reaction and Anaphylactic/Anaphylactoid Shock Conditions SMQs (MedDRA v12.1), no subject exposed to peramivir in any clinical trial setting was identified with anaphylaxis.

This reviewer also conducted a broad analysis using the above SMQs and the Angioedema SMQ. Table 35 lists the TEAEs identified by the broad SMQ analysis in the peramivir treatment groups; to these the following selected terms were added:

- Asthma
- Bronchospasm
- Conjunctival hyperaemia
- Conjunctivitis allergic
- Eosinophil count increased
- Eosinophil percentage increased
- Eosinophilia
- Hot flush
- Hypersensitivity
- Oedema
- Oedema peripheral
- Periorbital oedema
- Pharyngeal oedema
- Wheezing

Table 35: Anaphylaxis Broad SMQ Adverse Events (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Anaphylaxis SMQs (broad) plus Selected Preferred Terms	Number of Subjects (%)			
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=436)	Oseltamivir (N=365)
Any Anaphylactic Adverse Event	19 (3)	20 (3)	25 (6)	6 (2)
Asthma	2 (0.3)	1 (0.2)	4 (1)	1 (0.3)
Bronchospasm	1 (0.2)	0	1 (0.2)	0
Chest discomfort	0	1 (0.2)	0	1 (0.3)
Conjunctivitis allergic	1 (0.2)	0	0	0
Eosinophil count increased	1 (0.2)	1 (0.2)	0	1 (0.3)
Eosinophil percentage increased	4 (1)	5 (1)	3 (1)	0
Eosinophilia	0	1 (0.2)	4 (1)	0
Eyelid oedema	0	1 (0.2)	0	0
Hot flush	0	1 (0.2)	1 (0.2)	0
Hypersensitivity	1 (0.2)	0	0	0
Hypotension	0	1 (0.2)	0	1 (0.3)
Oedema peripheral	1 (0.2)	0	0	0
Pruritus	2 (0.3)	0	0	0
Rash	4 (1)	5 (1)	3 (1)	0
Rash pruritic	1 (0.2)	0	0	1 (0.3)
Renal failure	0	1 (0.2)	0	0
Urticaria	2 (0.3)	2 (0.3)	0	0
Wheezing	1 (0.2)	0	1 (0.2)	0

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

As shown in Table 35, the peramivir groups had minimally higher incidence of urticaria, rash, pruritus, and hypersensitivity events than the controls. However, no TEAE occurred in ≥1% of subjects in any treatment group, so the between-group differences were very small. Other than one TEAE of moderate 'asthma' in a subject treated with peramivir 300 mg IV (Subject 0815T0631.130.TDK02), none of the AEs identified by this analysis was serious. Mean time to onset for these events was 4-5 days in the peramivir groups, 3 days in the placebo group, and 5 days in the oseltamivir group. Mean duration of events was slightly greater in the peramivir groups (8-13 days) than in the placebo group (8 days), but less than in the oseltamivir group (15 days).

The one case of 'hypersensitivity', which was severe, and the two cases of 'hot flush' were discussed in Section 7.3.4. In addition, one event each of 'tongue oedema' and 'pharyngeal oedema' was identified using the broad Anaphylactic and Angioedema SMQs, respectively; both subjects were treated with IM peramivir 150 mg in Study

BCX1812-211. Neither case was compelling for anaphylaxis but both are discussed here:

- **Subject 056.022** - *MedDRA PT 'tongue oedema'* - This 42-year-old female in Canada, with past medical history of mild asthma, psoriasis, and seasonal rhinitis, was treated with 150 mg IM peramivir for influenza A/H3N2. On Day 10, she was reported to have moderate "oedema of base of tongue" that was not considered drug-related. The event was preceded by a TEAE of "left interior tooth abscess" on Day 8. No action was taken and the TEAE of tongue edema was reported as resolved 6 days later.

- **Subject 024.015** - *MedDRA PT 'pharyngeal oedema'* - This 33-year-old female in the United States, with past medical history of obesity, hypertension, depression, anxiety, and gestational diabetes, was treated with 150 mg IM peramivir for influenza A/H1N1. On Day 15, she was reported to have mild pharyngeal edema that was considered unlikely related to study drug. The event was preceded by a severe TEAE of 'blood glucose increased' on Day 5. Concomitant medications included paracetamol, cough syrup, naproxen, and promethazine with codeine. No action was taken with respect to the pharyngeal edema and the event was considered resolved by Day 20.

In summary, there is no compelling clinical evidence to suggest that peramivir causes severe hypersensitivity or anaphylaxis.

7) *Infusion Site Reactions*

During the development of peramivir, FDA requested information on phlebitis and necrosis events at the injection site. There were 3 subjects/events (2 events of mild vessel puncture site hematoma and 1 event of mild phlebitis) identified in the Applicant's response. Although no safety signal was seen, infusion site reactions became an event of special interest. Further, the event of "vascular pain" (Preferred Term 'angiopathy' MedDRA v12.1) was reported in postmarketing in Japan and added to RAPIACTA labeling in March 2011 (see Section 2.6). Most of the postmarketing events from Japan were nonserious and reported in children. Because placement of an IV line and infusion of fluids may be painful in and of itself, a role for peramivir could not be discerned from these spontaneous reports.

The formulation of peramivir under current review is for IV infusion. However, AE data for all subjects who received peramivir was reviewed, regardless of delivery route. Analysis was done by the Applicant using the narrow and broad terms of the Extravasation Events (Injections, Infusions, and Implants) SMQ (MedDRA v12.1), along with the selected PTs of 'phlebitis' and 'angiopathy'. This method was deemed acceptable by this reviewer.

No cases were identified by narrow SMQ search. By broad search, 13 events/subjects were identified with 'injection site pain' (PRV 300 mg 4 [0.6%], PRV 600 mg 5 [0.8%], and placebo 4 [0.9%]); all were in the BioCryst trials of IM peramivir. The vast majority

of these events were reported on Day 1; mean duration was 1-2 days. No subject in any trial of acute uncomplicated influenza experienced the TEAEs of 'angiopathy' or 'phlebitis'.

Review of the Phase 1 data yielded 66 cases of infusion site reactions, predominantly 'injection site pain'. Most of the events were related to IM administration and not IV. The incidence of these AEs was comparable between the peramivir and control groups and did not increase with increasing peramivir dosage. Two subjects in the single-dose trials experienced phlebitis.

In the hospitalized trials, there were only seven cases of infusion site reactions among IV peramivir-treated subjects; these were mostly related to angiopathy, phlebitis, or catheter-related complications. The incidence of these events was comparable to those seen in patients not receiving peramivir, suggesting that the events were probably related to IV infusion in general and not the study drug.

In summary, IV administration of peramivir may be associated with a very low rate of infusion site reactions, similar to that seen with infusion of any IV medication.

8) *Orthostatic Hypotension/Shock*

As noted in Section 2.6, shock was added to the clinically significant adverse drug reaction section of RAPIACTA labeling in March 2011. Wording in the Japanese package insert states:

> *"Shock (unknown incidence): Since shock (decreased blood pressure, facial pallor, cold sweat etc.) may occur, patients should be carefully observed. If any abnormality is observed, the therapy should be discontinued and appropriate measures taken."*

Based on postmarketing reports from Japan, FDA requested an integrated assessment of orthostatic hypotension and similar events from the clinical trials and postmarketing experience. A report was submitted to IND 69,038 on May 27, 2011. The Applicant's analysis focused on a range of events related to orthostatic hypotension and all potential sources of information were reviewed. The Applicant noted that the "shock" events reported by Japanese physicians were not clearly defined but appeared to be consistent with vasovagal reactions. The Applicant's review was unable to demonstrate an association between peramivir administration and orthostatic hypotension.

For the analysis of orthostatic hypotension and shock in the clinical trials, the Applicant used narrow terms from the Anaphylactic Reaction and Anaphylactic/Anaphylactoid Shock Conditions SMQs (MedDRA v12.1), along with the following selected PTs:

- Hypersensitivity
- Drug hypersensitivity
- Blood pressure orthostatic decreased
- Procedural hypotension
- Orthostatic hypotension
- Syncope
- Presyncope
- Loss of consciousness

The Applicant's methodology was acceptable; however, this reviewer also included the PT of 'dizziness' since this term was often used to code for events of lightheadedness.

By this method, 55 subjects across all treatment groups (including the PRV 150 mg group) were identified with potential events in the five controlled trials. Two-thirds of these subjects were in the BioCryst trials of IM peramivir. The most commonly reported TEAE was 'dizziness', followed by 'presyncope' or 'syncope', the latter two being predominantly vasovagal in nature and lasting only one day. Overall, the placebo group had the highest percentage of subjects with TEAEs (Table 36). No dose effect was noted for peramivir and none of the events was serious. The majority of events occurred on Day 1 or 2. Mean duration of events was greater in the peramivir groups than in the placebo group, but comparable to that of the oseltamivir group (PRV 300 mg 3 days, PRV 600 mg 5 days, placebo 1.8 days, oseltamivir 3.5 days).

Table 36: Orthostatic Hypotension/Shock Narrow SMQ Adverse Events (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Orthostatic Hypotension/Shock SMQs (narrow) plus Selected Preferred Terms	Number of Subjects (%)		
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=436)
Any Hypotensive/Shock Adverse Event	20 (3)	11 (2)	17 (3)
Dizziness	18 (3)	7 (1)	9 (2)
Hypersensitivity	1 (0.2)	0	0
Presyncope	0	3 (0.5)	5 (1)
Syncope	1 (0.2)	1 (0.2)	4 (1)

Note: subjects may have more than one adverse event term reported
Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

Since blood pressure is a clinical sign and reporting of an abnormal vital sign as an AE is at the discretion of the investigator, a categorical analysis of the blood pressure data from the five controlled trials was undertaken by this reviewer. The selection criterion for this analysis was decrease in systolic or diastolic blood pressure ≥ 20 mm Hg from baseline at any point post study drug administration. The results showed that 790 subjects had potentially clinically significant decreases in blood pressure during the reporting period, but the percentages were similar across treatment groups: PRV 300 mg 35%; PRV 600 mg 36%; placebo 33%; oseltamivir 42%.

About a quarter of these subjects experienced a drop in blood pressure on Day 1, with similar incidence across the four treatment groups (range 7.4-9.5%), and no difference was noted between the two peramivir dose groups (PRV 300 mg 8.5%, PRV 600 mg 9.5%). There was a 2-fold increase in Day 1 cases between subjects treated with PRV IM (5%) and those treated with PRV IV (10.5%), but a similar effect was noted in the placebo group (IM 5.6%, IV 15%) suggesting that the difference may have been related to route of administration rather than study drug.

In the Phase 1 trials, 15 subjects (2%) treated with peramivir experienced an orthostatic hypotension/shock event compared to 1 subject (3%) who received placebo. All of these events were presyncope. In the hospitalized trials, the overall number of subjects experiencing orthostatic hypotension events was small and no differences could be discerned between treatment groups.

In summary, most of the syncope or presyncope events noted in the clinical trial database were vasovagal responses and occurred predominantly with IM injections. Moreover, the overall incidence of these events, as well as the incidence of vital sign changes, was balanced between peramivir and the control groups. As such, there does not appear to be a correlation between peramivir administration and hypotensive shock.

9) Neuropsychiatric Events

As noted in Section 2.4, neuropsychiatric events have been reported in the postmarketing experience with other NAIs, primarily oseltamivir. The events have occurred predominantly in Japanese pediatric patients. Because influenza itself can be associated with delirium or hallucinations, and the reports have occurred in the postmarketing setting, a definitive relationship between NAIs and these types of events has not been established. Regardless, the package inserts of other NAIs contain precautionary language regarding abnormal behavior because some subjects were injured or even died during these events. For this reason, TEAEs indicative of neuropsychiatric events were monitored in the peramivir development program.

For the analysis of neuropsychiatric events, this reviewer used broad and narrow terms in the following SMQs (version 12.1):

- Dementia, Depression (excl Suicide and Self Injury) SMQ
- Depression and Suicide/Self-Injury SMQ
- Hostility/Aggression SMQ
- Noninfectious Encephalitis SMQ
- Noninfectious Encephalopathy/Delirium SMQ
- Psychosis and Psychotic Disorders SMQ

This analysis was broader than one performed by the Applicant, which only used the Noninfectious Encephalopathy/Delirium SMQ.

By narrow SMQ, two subjects were identified in the five adult trials of acute uncomplicated influenza with 1 event each of 'anger' and 'depressed mood'; both were treated with placebo. By broad SMQ, 13 additional TEAEs/subjects were identified in the peramivir (all doses) and placebo groups; no subjects treated with oseltamivir were identified with a neuropsychiatric event by this method. The events in the PRV 300 mg, PRV 600 mg, and placebo groups are displayed in Table 37.

Analysis by the "Psychiatric Disorders" SOC yielded five additional terms, with no distinct pattern between groups: 'insomnia', 'anxiety', 'depressed mood', 'nightmare', and 'panic reaction'. These terms were added to Table 37 for the sake of completeness. One oseltamivir-treated subject (0.3%) had a TEAE of 'insomnia'.

Table 37: Neuropsychiatric Adverse Events (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Neuropsychiatric SMQs (broad) plus Selected Preferred Terms	Number of Subjects (%)		
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=436)
Any Neuropsychiatric Adverse Event	13 (2)	4 (1)	9 (2)
Anger	0	0	1 (0.2)
Anxiety	1 (0.2)	0	0
Depressed level of consciousness	1 (0.2)	0	0
Depressed mood	0	0	1 (0.2)
Dysphagia	0	0	1 (0.2)
Feeling abnormal	2 (0.3)	1 (0.2)	1 (0.2)
Insomnia	3 (0.5)	3 (0.5)	3 (1)
Musculoskeletal stiffness	2 (0.3)	0	0
Nightmare	0	0	1 (0.2)
Panic reaction	0	0	1 (0.2)
Poor quality sleep	1 (0.2)	0	0
Skin laceration	1 (0.2)	0	0
Somnolence	2 (0.3)	0	0

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

None of these events was serious. Mean time to AE onset was 4-6 days in the peramivir groups, 4 days in the placebo group and 3 days in the one oseltamivir subject. Mean duration of events was 4-5 days for all groups except the PRV 600 mg group where the mean duration of events was 16 days; this group, however, had only 4 subjects with neuropsychiatric TEAEs and the differences were driven by two subjects with prolonged TEAEs of 'insomnia' (39 days) and 'feeling abnormal' (18 days; verbatim term "fuzzy head'), both of which were mild.

The event of 'skin laceration', identified by the broad Hostility/Aggression SMQ, was a laceration to the left index finger and thus seemed less likely to represent an event of self-harm. Similarly, the two events of 'musculoskeletal stiffness' ("stiff neck" and "stiff shoulder") were identified by the broad Noninfectious Encephalitis SMQ, but did not appear to be indicative of true neuropsychiatric events. The TEAEs of 'feeling abnormal', observed across the peramivir and placebo groups, were identified by the broad Dementia SMQ; this PT was used to code such diverse verbatim terms as "dazed feeling", "dazedness", "floating", and "strange feeling".

Whether by MedDRA SMQ or SOC analysis, however, no TEAEs were reported in any adult trial of acute uncomplicated influenza consistent with delirium, suicidality, or the type of abnormal behaviors described in the oseltamivir postmarketing experience. Overall, given the paucity of events in these trials, no clear relationship could be established between peramivir administration and neuropsychiatric events in adults with acute uncomplicated influenza.

In Phase 1, there were 15 peramivir-treated subjects who experienced a neuropsychiatric event: 10 (1.7%) in the single-dose trials and 5 (5.5%) in the multiple-dose trials. These TEAEs included 'somnolence' (12 subjects), 'disturbance in attention' (1 subject), 'agitation' (1 subject), and 'muscular weakness' (1 subject). No subjects who received placebo, other active study drug, or oseltamivir experienced a neuropsychiatric event in Phase 1. Again, these types of AEs were not consistent with the abnormal behaviors described in NAI labeling.

In the Japanese pediatric trial in acute uncomplicated influenza (Study 0918T0633), four subjects (3.4%) experienced neuropsychiatric TEAEs: three (2.6%) had 'abnormal behaviour' and one (0.9%) had 'encephalopathy'. Please see Section 7.6.3 for further details.

Neuropsychiatric AEs in the trials of hospitalized patients were difficult to interpret as they were usually confounded by underlying influenza disease. Moreover, AEs such as 'delirium' or 'confused state' tended to occur in elderly subjects, which is not an uncommon occurrence in hospitalized geriatric patients.

In summary, there is little clinical data to suggest an association between peramivir and abnormal behavior in adults with acute uncomplicated influenza. It is unclear if such a relationship exists in children since such events were reported in an uncontrolled trial. Labeling for peramivir should contain a Warning and Precaution statement consistent with drug class labeling for NAIs.

10) *Seizures*

An analysis of neurological events was conducted by this reviewer because of convulsion events reported among peramivir-treated subjects in Study BCX1812-303, the open-label trial of IV peramivir in hospitalized patients with influenza A/H1N1pdm09, as well as in the Japanese pediatric Study 0916T0633.

Details of two convulsion cases in Study BCX1812-303 (Subjects 131.001 and 153.013) were reviewed. In both cases, the seizure events were confounded by factors related to severe influenza illness, underlying comorbid conditions, and other complications related to critical illness. Both subjects (in their 50's) had respiratory failure at presentation and were intubated and admitted to the ICU early in their hospital course, before initiating IV peramivir.

In Study 0918T033, convulsion was noted in a 5-year-old boy treated with a single dose of peramivir at 10 mg/kg (180 mg). His narrative is as follows:

- **Subject 3BH007** was already very ill at presentation with fever (temperature 38.7^{o}C) and respiratory rate > 40/min. He was diagnosed with influenza A by RAT, later determined to be novel 2009 influenza A/H1N1. Within a few hours after receiving peramivir, his condition deteriorated with respiratory rate 46/min and SpO_2 87%. The subject was discontinued from the study and urgently transferred to a hospital, where a chest X-ray showed a left lower reticular shadow consistent with pneumonia. He had a convulsion shortly after arrival at the other hospital (approximately 4 hours after peramivir infusion) with decreased consciousness. A head CT and MRI were normal and EEG showed high voltage slow waves. Spinal fluid was collected (results not reported). The subject was diagnosed with influenza encephalopathy and steroid pulse therapy was started. He improved on ampicillin/sulbactam and steroid therapy. No further convulsions were noted and follow-up EEG and chest X-ray both showed improvement. He was discharged from hospital on the (b) (6) day.

There have also been postmarketing reports of convulsion in Japan. One such event occurred in a 72-year-old woman with advanced dementia diagnosed with influenza and given peramivir. One day later, she developed a seizure and was taken to hospital where she was treated with diazepam. Her temperature at the time of the event was 39°C.

Other postmarketing seizure events have involved children, and are briefly described here:

- A 9-year-old girl with history of febrile seizures received peramivir for influenza and developed a seizure during the infusion. Her temperature was 39°C, and the event was considered a febrile seizure by her treating physician.
- A 7-year-old boy developed influenza with fever of 40.2°C. He was treated with peramivir for 2 consecutive days due to persistent high fever and developed a tonic-clonic seizure later in the day after the second dose, although the reporter stated that there was no

fever at the time. An EEG was negative. The high fever returned, and treatment with antibiotics was started. Three days after the start of peramivir, the fever resolved.

- An 11- year-old girl, with a history of childhood febrile seizures, developed tonic convulsion during peramivir infusion for influenza B infection. She had a very high fever (38-39.5^{o} C) for several hours prior to receiving peramivir and the onset of seizure. She received a diazepam suppository and the seizure abated. Subsequent MRI did not reveal evidence for encephalitis. There was no recurrence of the seizure. Other than the childhood history of febrile seizure and the underlying influenza, no risk factors were noted. The case was considered possibly related to peramivir because of the temporal association and the patient's age, which makes febrile seizure less likely, although not impossible.

Using the broad and narrow terms from the Convulsion, Noninfectious Encephalitis, Noninfectious Encephalopathy/Delirium, and Noninfectious Meningitis SMQs, this reviewer was unable to identify any potential seizure events in any of the 7 trials of peramivir in acute uncomplicated influenza, whether in adults or pediatrics.

In summary, there is little clinical data to suggest that peramivir use is associated with seizure. Toxicology data suggests there is very little central nervous system penetration of peramivir. The few events of convulsion reported with peramivir have mostly been consistent with febrile seizures and/or occurred in patients infected with influenza who may have had a pre-existing low seizure threshold, such as the severely ill and hospitalized, the young, or the elderly with pre-existing neurologic disorders. Influenza itself can be associated with a variety of neurologic and behavioral symptoms which can include seizures, hallucinations, delirium, and abnormal behavior. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

11) *Hemorrhagic Colitis*

Hemorrhagic colitis appears in the prescribing information for oseltamivir as a postmarketing event and is listed as an event seen with other NAIs in labeling for RAPIACTA in Japan. There were also five spontaneous SAE reports of enterocolitis haemorrhagic associated with RAPIACTA reported to Shionogi in postmarketing. All of the cases were heavily confounded when reviewed, primarily with anticoagulant use, NSAID use, or history of ischemia. In the few cases where endoscopy was performed, the findings were suggestive of ischemia.

For the analysis of hemorrhagic colitis events, the Applicant used a customized query of selected PTs that included: 'diarrhoea haemorrhagic', 'enterocolitis haemorrhagic', 'haematochezia', 'large intestinal haemorrhage', 'lower gastrointestinal haemorrhage', 'proctitis haemorrhagic', and 'rectal haemorrhage' (MedDRA v12.1). By this method, one 40-year-old male subject in Study BCX1812-212 (Subject 410.003, treated with peramivir 600 mg IM) was identified with a nonserious TEAE of moderate 'haematochezia' (verbatim term: "bloody stools"), reported as beginning on Day 12 and

resolving by Day 17. The event was precipitated by severe 'diarrhoea' and 'hot flush' on Days 2 and 3, respectively; both of which resolved by Day 8. None of these TEAEs was considered related to study drug by the investigator. Review of the subject's clinical data revealed that all laboratory tests and vital signs remained normal throughout study.

This reviewer conducted an additional analysis using narrow terms from the following MedDRA SMQs:

- Gastrointestinal haemorrhage (SMQ)
- Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ)
- Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)
- Gastrointestinal ulceration (SMQ)
- Haemorrhage laboratory terms (SMQ)
- Haemorrhage terms (excl laboratory terms) (SMQ)
- Haemorrhages (SMQ)

In addition to the aforementioned case of 'haematochezia', the narrow SMQ search yielded only two subjects with 'occult blood positive', both treated with peramivir 300 mg IV in Shionogi-sponsored trials. Neither case was compelling for hemorrhagic colitis based on the available clinical data. A broad search using these same SMQs resulted in a small number of additional cases of 'abdominal discomfort' or 'enterocolitis', none of which were consistent with hemorrhagic colitis. Risk differences (per hundred) for any of the above gastrointestinal-specific SMQs, or any of the Preferred Terms identified by the broad search, were less than 0.5% between peramivir (any dose level) and placebo.

There were no reports of hemorrhagic colitis in any of the Phase 1 trials, or in the pediatric study in Japan. In the hospitalized trials, there were two subjects who experienced hematochezia, one treated with peramivir plus oseltamivir and one treated with oseltamivir alone; both cases were confounded by underlying illness.

In summary, the clinical trial data regarding hemorrhagic colitis are limited and not compelling for a correlation with peramivir.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This section reviews the common TEAEs observed with peramivir 300 mg or 600 mg in the five controlled trials of adults with acute uncomplicated influenza. For this integrated analysis, all TEAEs were included, irrespective of investigator assessment of causality.

Nearly half of all treated subjects with acute uncomplicated influenza experienced at least one TEAE, with similar proportions across treatment groups. Overall, the most

common TEAE by MedDRA Preferred Term was ‘diarrhea’, with comparable incidence in each treatment group.

For both the peramivir 300 mg and 600 mg treatment groups, the majority of TEAEs were reported under the “Investigations” SOC, with ‘neutrophil count decrease’ being the most common PT for that SOC (PRV 300 6%, PRV 600 6%, placebo 0). As noted in Section 7.3.5, the majority of subjects with ‘neutrophil count decreased’ or ‘neutropenia’ were in the Shionogi trials, particularly Study 0815T0631. The Shionogi investigators tended to code laboratory abnormalities as AEs more often than BioCryst investigators. As also noted in Section 7.3.5, when laboratory data were analyzed, there were no significant differences in the incidence of laboratory-confirmed leukopenia or neutropenia between the peramivir and oseltamivir groups of Study 0815T0631. Further, when data from Study 0815T0631 were excluded, the differences between the peramivir and placebo groups with respect to leukocyte or neutrophil laboratory abnormalities were less.

In the integrated analysis, TEAEs under the MedDRA HLT “Urinalysis NEC” were reported more frequently in the peramivir treatment groups compared with placebo, with a greater risk difference (per hundred) versus placebo observed in the peramivir 300 mg group than in the peramivir 600 mg group (3.5 and 1.5, respectively). Most of the TEAEs under this HLT were consistent with ‘white blood cells urine present’. Of note, all subjects with TEAEs under this HLT were in the Shionogi trials. Further, as noted in Section 7.3.5 “Nephrotoxicity”, when urinalysis data were evaluated, there was no noted increase in the incidence of pyuria with peramivir treatment compared with placebo.

In addition to the neutrophil count and pyuria events noted above, there was a slightly greater incidence of ‘blood phosphorus decreased’ events with peramivir 300 mg compared with placebo (2.1% versus 0.5%, respectively). With peramivir 600 mg, there was a slightly greater incidence of ‘increased blood creatinine phosphokinase’ events compared with placebo (2.1% versus 0.5%, respectively). Otherwise, there were no significant risk differences (≥ 1.5 per hundred) noted between the peramivir treatment groups and placebo with respect to gastrointestinal disorders, liver function tests, nervous system disorders, psychiatric disorders or rash events.

Table 38 provides a summary of all TEAEs occurring in ≥ 1% of peramivir-treated subjects (300 mg and 600 mg) across the five controlled trials. Events are listed by MedDRA PT and grouped by SOC. Some events are also grouped by MedDRA HLGT or HLT, or in some cases only the higher level term is reported, to assess for clinically relevant safety trends. Incidence rates observed in the oseltamivir treatment group of Study 0815T0631 are included as reference.

Table 38: Treatment-Emergent Adverse Events, Incidence ≥ 1% in Peramivir-Treated Subjects (300 mg or 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Common Adverse Events	Number of Subjects (%)			
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=436)	OSE (N=365)
Any Adverse Event	325 (52)	321 (48)	223 (51)	178 (49)
Gastrointestinal disorders	84 (13)	84 (13)	67 (15)	66 (18)
Diarrhoea	48 (8)	51 (8)	31 (7)	27 (8)
Nausea	24 (4)	21 (3)	20 (5)	20 (6)
Vomiting	8 (1)	13 (2)	10 (2)	15 (4)
Infections and infestations	35 (6)	47 (7)	33 (8)	30 (8)
HLT Upper respiratory tract infections	8 (1)	19 (3)	12 (3)	11 (3)
Bronchitis	8 (1)	5 (1)	3 (1)	6 (2)
Nasopharyngitis	4 (1)	10 (2)	7 (2)	6 (2)
HLT Herpes viral infections	4 (1)	13 (2)	4 (1)	7 (2)
Investigations	205 (33)	208 (31)	102 (23)	106 (29)
HLGT Haematology investigations (incl blood groups)	102 (16)	85 (13)	49 (11)	36 (10)
Neutrophil count decreased	37 (6)	38 (6)	0	32 (9)
Neutrophil percentage decreased	1 (0.2)	1 (0.2)	0	0
Lymphocyte morphology abnormal	11 (2)	4 (1)	7 (2)	1 (0.3)
Lymphocyte percentage increased	14 (2)	14 (2)	5 (1)	0
Monocyte percentage increased	20 (3)	18 (3)	31 (7)	0
Haemoglobin decreased	7 (1)	3 (0.5)	3 (1)	1 (0.3)
White blood cell count decreased	12 (2)	13 (2)	7 (2)	2 (0.5)
HLT Liver function Analyses	31 (5)	36 (5)	22 (5)	7 (2)
Alanine aminotransferase increased	17 (3)	18 (3)	13 (3)	5 (1)
Aspartate aminotransferase increased	7 (1)	16 (2)	11 (3)	2 (0.5)
Blood bilirubin increased	8 (1)	9 (1)	7 (2)	0
HLT Urinalyses NEC	68 (11)	59 (9)	32 (7)	47 (13)
Blood urine present	8 (1)	7 (1)	1 (0.2)	2 (0.5)
Glucose urine present	10 (2)	7 (1)	2 (0.5)	8 (2)
Protein urine present	27 (4)	27 (4)	20 (5)	21 (6)
Red blood cells urine positive	6 (1)	7 (1)	1 (0.2)	6 (2)
White blood cells urine positive	21 (3)	18 (3)	8 (2)	16 (4)
HLT Protein analyses NEC	19 (3)	17 (3)	22 (5)	2 (0.5)
Alpha 1 microglobulin urine increased	6 (1)	6 (1)	6 (1)	0
Beta 2 microglobulin urine increased	14 (2)	8 (1)	2 (0.5)	0
Blood creatine phosphokinase increased	6 (1)	14 (2)	2 (0.5)	1 (0.3)
Blood glucose increased	29 (5)	32 (5)	21 (5)	12 (3)
Blood phosphorus decreased	13 (2)	7 (1)	2 (0.5)	1 (0.3)
Blood phosphorus increased	7 (1)	3 (0.5)	4 (1)	0

Beta-N-acetyl-D-glucosaminidase increased	9 (1)	5 (1)	5 (1)	0
Electrocardiogram QT prolonged	7 (1)	9 (1)	3 (1)	10 (3)
Nervous system disorders	34 (5)	18 (3)	33 (8)	8 (2)
Dizziness	18 (3)	7 (1)	9 (2)	1 (0.3)

Abbreviations: HLGT = High Level Group Term; HLT = High Level Term; OSE = oseltamivir
Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Analysis of Safety (ISS)

Table 39 displays the most common TEAEs associated with peramivir treatment, defined as incidence ≥ 2% in peramivir-treated subjects (either dose group) and occurring at a greater rate on peramivir than placebo. This table differs from that proposed by the Applicant for labeling due to a) inclusion of the peramivir 300 mg dose group, b) elimination of data from Study 0816T0632, and c) elimination of subjects from the BioCryst clinical trial sites that failed FDA inspection (see Section 3.2); (b) (4) (b) (4) The most common TEAE associated with peramivir treatment by this method was diarrhea; the remaining AEs were laboratory-related AEs, the reporting of which varied by clinical trial. Final labeling will separate the laboratory abnormalities from clinical events.

Table 39: Common Treatment-Emergent Adverse Events Incidence ≥ 2% in Peramivir-Treated Subjects (300 mg or 600 mg) and Incidence Greater Than in Placebo Groups - Controlled Trials in Acute Uncomplicated Influenza

Common Adverse Events	Number of Subjects (%)			
	Peramivir 300 mg (N=627)	Peramivir 600 mg (N=664)	Placebo (N=436)	Oseltamivir (N=365)
Diarrhoea	48 (8)	51 (8)	31 (7)	27 (7)
Neutrophil count decreased	37 (6)	38 (6)	0	32 (9)
Blood glucose increased	29 (5)	32 (5)	21 (5)	12 (3)
White blood cells urine positive	21 (3)	18 (3)	8 (2)	16 (4)
Blood creatine phosphokinase increased	6 (1)	14 (2)	2 (0.5)	1 (0.3)
Lymphocyte percentage increased	14 (2)	14 (2)	5 (1)	0
Blood phosphorus decreased	13 (2)	7 (1)	2 (0.5)	1 (0.3)
Dizziness	18 (3)	7 (1)	9 (2)	1 (0.3)

Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

7.4.2 Laboratory Findings

Laboratory abnormalities that were Grade 2-4 were not commonly seen with peramivir treatment, generally occurring in less than 1% of subjects for any given parameter. Grade 2-3 decreases in hemoglobin were noted with slightly more frequency with peramivir 300 mg or 600 mg treatment than with placebo or oseltamivir, although their

overall incidence was low (Table 40); other hematological toxicities occurred at a comparable or lower incidence in the peramivir groups than in the placebo group. (See Section 7.3.5 for analysis of laboratory abnormalities related to leukopenia and neutropenia.)

Table 40: Treatment-Emergent Hematology Abnormalities by Maximum Toxicity Grade (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Maximum Toxicity Grade	Peramivir 300 mg	Peramivir 600 mg	Placebo	Oseltamivir
Hemoglobin (g/dL)	**N=617**	**N=657**	**N=430**	**N=362**
Any Grade	19 (3)	21 (3)	14 (3)	5 (1)
Grade 1 (10.0 - 10.9 g/dL), n (%)	14 (2)	12 (2)	11 (3)	4 (1)
Grade 2 (9.0 - 9.9 g/dL), n (%)	4 (1)	5 (1)	2 (0.5)	1 (0.3)
Grade 3 (7.0 - 8.9 g/dL), n (%)	1 (0.2)	4 (1)	0	0
Grade 4 (< 7.0 g/dL), n (%)	0	0	1 (0.2)	0
Lymphocytes (10^3/µL)	**N=518**	**N=556**	**N=362**	**N=325**
Any Grade	3 (1)	5 (1)	6 (2)	1 (0.3)
Grade 1 (0.6 - 0.65 x10^3/µL), n (%)	1 (0.2)	1 (0.2)	0	0
Grade 2 (0.5 - 0.599 x10^3/µL), n (%)	1 (0.2)	0	3 (1)	0
Grade 3 (0.35 - 0.499 x10^3/µL), n (%)	1 (0.2)	4 (1)	2 (1)	1 (0.3)
Grade 4 (< 0.35 x10^3/µL), n (%)	0	0	1 (0.3)	0
Platelets (10^3/uL)	**N=615**	**N=650**	**N=423**	**N=361**
Any Grade	9 (2)	12 (2)	9 (2)	4 (1)
Grade 1 (100 -124.999 x10^3/µL), n (%)	8 (1)	8 (1)	6 (1)	4 (1)
Grade 2 (50 - 99.999 x10^3/µL), n (%)	1 (0.2)	4 (1)	3 (1)	0

N = number of subjects with baseline laboratory values
Source: created by clinical reviewer using laboratory analysis dataset (ADLB.xpt) – Integrated Summary of Safety (ISS)

With respect to serum chemistries, other than hyperglycemia (non-fasted) and low serum bicarbonate, no laboratory toxicity was observed more frequently in the peramivir groups than in the placebo group (Table 41). In the case of hyperglycemia, the incidence of graded high serum glucose was comparable between the peramivir and oseltamivir groups. The reasons for the increased incidence of hypocapnia seen with peramivir treatment are not clear, but it should be noted that most of the cases were Grade 1 and the sample size was small as the Shionogi trials did not collect serum bicarbonate data.

Table 41: Treatment-Emergent Chemistry Abnormalities by Maximum Toxicity Grade (Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Maximum Toxicity Grade	Peramivir 300 mg	Peramivir 600 mg	Placebo	Oseltamivir
Glucose, serum, high (mg/dL)	**N=624**	**N=660**	**N=433**	**N=364**
Any Grade	148 (24)	150 (23)	84 (19)	80 (22)

Grade 1 (116 - 160 mg/dL), n (%)	124 (20)	120 (18)	70 (16)	68 (19)
Grade 2 (161 - 250 mg/dL), n (%)	22 (4)	24 (4)	10 (2)	11 (3)
Grade 3 (251 - 500 mg/dL), n (%)	2 (0.3)	6 (1)	2 (0.5)	1 (0.3)
Grade 4 (> 500 mg/dL), n (%)	0	0	2 (0.5)	0
Glucose, serum, low (mg/dL)	**N=624**	**N=660**	**N=433**	**N=364**
Any Grade	15 (2)	16 (2)	13 (3)	5 (1)
Grade 1 (55 - 64 mg/dL), n (%)	11 (2)	13 (2)	8 (2)	2 (0.5)
Grade 2 (40 - 54 mg/dL), n (%)	4 (1)	2 (0.3)	5 (1)	3 (1)
Grade 3 (30 - 39 mg/dL), n (%)	0	1 (0.2)	0	0
Phosphate, low (mg/dL)	**N=625**	**N=658**	**N=434**	**N=362**
Any Grade	45 (7)	48 (7)	49 (11)	20 (6)
Grade 1 (2.5 mg/dL - < LLN), n (%)	16 (3)	16 (3)	11 (3)	4 (1)
Grade 2 (2.0 - 2.4 mg/dL), n (%)	25 (4)	29 (4)	36 (8)	16 (4)
Grade 3 (1.0 - 1.9 mg/dL), n (%)	4 (1)	3 (0.5)	2 (0.5)	0
Magnesium, low (mEq/L)	**N=627**	**N=663**	**N=434**	**N=364**
Any Grade	3 (0.5)	12 (2)	24 (6)	1 (0.3)
Grade 1 (1.2 - 1.4 mEq/L), n (%)	3 (0.5)	12 (2)	23 (5)	1 (0.3)
Grade 2 (0.9 - 1.1 mEq/L), n (%)	0	0	1 (0.2)	0
Potassium, high (mEq/L)	**N=620**	**N=655**	**N=432**	**N=359**
Any Grade	2 (0.3)	6 (1)	4 (1)	0
Grade 1 (5.6 - 6.0 mEq/L), n (%)	2 (0.3)	5 (1)	3 (1)	0
Grade 2 (6.1 - 6.5 mEq/L), n (%)	0	1 (0.2)	0	0
Grade 3 (6.6 - 7.0 mEq/L), n (%)	0	0	1 (0.2)	0
Potassium, low (mEq/L)	**N=620**	**N=655**	**N=432**	**N=359**
Any Grade	17 (3)	18 (3)	21 (5)	22 (6)
Grade 1 (3.0 - 3.4 mEq/L), n (%)	17 (3)	15 (2)	21 (5)	22 (6)
Grade 2 (2.5 - 2.9 mEq/L), n (%)	0	3 (0.5)	0	0
Bicarbonate, low (mEq/L)	**N=163**	**N=200**	**N=333**	**--**
Any Grade	4 (3)	19 (10)	19 (6)	--
Grade 1 (16.0 mEq/L - < LLN), n (%)	1 (1)	18 (9)	16 (5)	--
Grade 2 (11.0 - 15.9 mEq/L), n (%)	3 (2)	1 (0.5)	3 (1)	--
Calcium, high (mg/dL)	**N=627**	**N=664**	**N=434**	**N=364**
Any Grade	2 (0.3)	4 (1)	6 (1)	0
Grade 1 (10.6 -11.5 mg/dL), n (%)	2 (0.3)	4 (1)	5 (1)	0
Grade 2 (11.6 - 12.5 mg/dL), n (%)	0	0	1 (0.2)	0
Calcium, low (mg/dL)	**N=627**	**N=664**	**N=434**	**N=364**
Any Grade	13 (2)	11 (2)	16 (4)	8 (2)
Grade 1 (7.8 - 8.4 mg/dL), n (%)	13 (2)	10 (2)	15 (4)	8 (2)
Grade 2 (7.0 - 7.7 mg/dL), n (%)	0	1 (0.2)	0	0
Grade 3 (6.1 -6.9 mg/dL), n (%)	0	0	1 (0.2)	0

N = number of subjects with baseline laboratory values
Source: created by clinical reviewer using laboratory analysis dataset (ADLB.xpt) – Integrated Summary of Safety (ISS)

7.4.3 Vital Signs

Vital sign changes were similar across all subjects in the adult trials of uncomplicated influenza. While some potentially clinically significant values were reported, their incidence was comparable between treatment groups (see Section 7.3.5 for discussion of blood pressure decreases).

7.4.4 Electrocardiograms (ECGs)

All subjects in the Shionogi adult trials of IV peramivir in acute uncomplicated influenza (Studies 0722T0622 and 0815T0631) had 12-lead ECGs performed at Screening, Day 1 (post-dose immediately after completion of infusion), Day 3, and at the completion of study or discontinuation. ECG results were interpreted by a central facility. A total of 29 subjects (2%) had TEAEs of 'electrocardiogram QT prolonged' reported; the incidence of these events was comparable across treatment groups: PRV 300 mg 7 (1%), PRV 600 mg 9 (1%), placebo 3 (1%), oseltamivir 10 (3%). Most of these QTc prolongations were minor and two-thirds were noted at the Day 6 visit or beyond, arguing against a causal relationship to study drug. Only two events were considered possibly related to study drug:

- **Subject CF1.157-1** - was treated with 300 mg IV peramivir in Study 0722T0621 and had a 61.5 msec increase in QTcF from baseline on Day 3; the QTc returned to near baseline value by the end of study. Because the prolongation occurred 2 days after dosing, it was not possible to rule out a causal relationship.

- **Subject 122.TAR01** - was treated with 600 mg IV peramivir in Study 0815T0631 had QTcF prolongation of 62 msec from baseline recorded on Day 9. The investigator believed this event to be related to the underlying disease, but as a causal relationship with study drug could not be completely ruled out, this was considered to be an adverse drug reaction. This patient had no abnormal ECG findings other than QT prolonged and developed no other adverse events. Considering that this event first occurred on Day 9, the influence of peramivir was thought to be negligible.

In the BioCryst trials of IM peramivir, ECGs were performed at the Screening/Baseline visit only, thus no TEAEs related to ECG findings could be reported.

Please refer to Section 7.4.5, 'Thorough QT Study' for a description of the dedicated through QT study conducted in support of this application.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Study

Study BCX1812-106 was a single-center, randomized, double-blind, double-dummy, Phase 1 placebo- and active-controlled, 4-period, crossover thorough QT (TQT) study

that evaluated two single doses of IV peramivir (600 mg and 1200 mg) administered over 30 minutes versus moxifloxacin 400 mg tablets and placebo (IV and tablet). All enrolled subjects were to receive each of the 4 treatments in the order determined by a randomly assigned treatment sequence. A total of 52 healthy subjects (26 males and 26 females) were enrolled and 49 subjects completed the study.

The TQT study report was submitted to IND 69,038 in December 2009 and reviewed by the FDA Interdisciplinary Review Team (IRT) for QT Studies. The IRT concluded that no significant QTc prolongation effect of peramivir (600mg and 1200 mg) was detected in this study. The largest upper bounds of the 2-sided 90% CI for the mean difference between peramivir (600 mg and 1200 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated indicating that assay sensitivity was established. Peramivir was found to be safe and well tolerated at both doses and neither therapeutic nor supratherapeutic doses were associated with any electrocardiographic abnormality. There was no increase in QTc with increasing doses of peramivir. A summary of findings is presented in Table 42.

Table 42: Point Estimates and the 90% CIs Corresponding to Largest Upper Bounds for Peramivir (600 mg and 1200 mg) and Largest Lower Bound for Moxifloxacin - Thorough QT Study BCX1812-106 (FDA Analysis)

Treatment	Time	ΔΔQTcF (ms)	90% CI (ms)
Peramivir 600 mg	8.5 hour	2.0	(-0.2, 4.1)
Peramivir 1200 mg	35 minutes	0.9	(-1.3, 3.0)
Moxifloxacin 400 mg*	2.5 hour	12.2	(10.1, 14.3)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 13 timepoints is 8.8 ms.
Source: Table 1 of IRT Consultation: Thorough QT Study Review (IND 69,038 SDN 133)

Renal Impairment Study

Study BCX1812-105 was a U.S. Phase 1 open-label PK trial of IV peramivir in adults with impaired renal function. Thirty (30) subjects were enrolled into 5 cohorts based on renal function – Cohort 1 normal renal function (creatinine clearance [CrCl] > 80 mL/min); Cohort 2 – mild renal impairment (CrCl 50-80 mL/min), Cohort 3 - moderate renal impairment (CrCl 30-49 mL/min), Cohort 4 - severe renal impairment (CrCl < 30 mL/min), and Cohort 5 - end-stage renal disease (ESRD) requiring chronic hemodialysis. A single dose of peramivir (2 mg/kg) was administered to all subjects except those having ESRD, who received a single dose of 2 mg/kg on two separate occasions (2 hours before hemodialysis and at the completion of a subsequent hemodialysis). Mean age of study participants was 56.1 years, 50% were Caucasian, 43% were African American, 3.3% were Hispanic, and there was an equal number of

men and women. The cohorts were generally comparable with respect to median age and weight, except Cohort 4 had a higher median age at 63.5 years.

Although this was a non-comparative trial and the evaluated dose of peramivir was lower than the recommended dose of 600 mg proposed in this application, the types and frequencies of AEs were similar across all 5 study cohorts. The most frequently reported AEs were headache and diarrhea, each reported by 10% of subjects. Serial laboratory and ECG assessments and sequential 24-hour urine collections revealed no important changes within any of the 5 cohorts. The clinical laboratory data, other than the expected abnormalities consistent with chronic renal impairment, did not suggest any adverse findings associated with exposure to peramivir in this population. Please see the Clinical Pharmacology Review by Dr. Leslie Chinn for review of the PK findings from this trial.

Elderly Safety Study

Study BXC1812-104 was U.S. Phase 1 double-blind, multiple-dose, randomized, placebo-controlled, single-center study that evaluated the safety and PK of IV peramivir in healthy male and female subjects aged ≥ 65 years. The study was designed in two parts. In Part I, 20 subjects received 4 mg/kg peramivir twice daily on Day 1. If any of these 20 subjects had a urinalysis dipstick protein result of ≥ 1+ obtained on Day 2 or urine protein > 150 mg/24 hours from either the Baseline to Day 1 (24-hour urine collection), or the 24-hour urine collection from Day 1 to Day 2, the subject was excluded from further participation. In Part II, 16 subjects went on to receive multiple-day dosing of peramivir (two 4 mg/kg infusions administered 12 hours apart, for a total daily dose of 8 mg/kg) or placebo over either 5 or 10 consecutive days (Group A and Group B, respectively); randomization in the Part II cohorts was 3:1. Mean age of enrolled subjects was 70.1 years in Part I and 69.8 years in Part II. There was an equal distribution of men and women in Part I; in Part II, 62.5% were female. Overall, 95% of subjects were Caucasian. Subject weights ranged from 52.9 to 105.3 kg and medical histories were consistent with healthy members of this age group.

In this trial, twice-daily dosing of peramivir for either a single day or over 5 or 10 consecutive days was well tolerated in healthy elderly subjects. Adverse events were noted in 25% of subjects in Part I, 83% of peramivir-treated subjects in Part II Group A (5 days) and 67% of peramivir-treated subjects in Part II Group B (10 days). Three subjects enrolled in Part I were ineligible to continue to Part II due increased urine protein excretion (>150 mg/24 hours); one of these subjects also had a TEAE of ‘hematuria’. The most commonly reported TEAEs in Part II Group A were diarrhea (3 peramivir subjects [50%]) and constipation (2 peramivir subjects [33.3%] and 1 placebo subject [50%]); in Part II Group B, they were headache (1 peramivir subject [16.7%]), and ECG prolonged QTc interval (2 peramivir subjects [33.3%]). None of the subjects had treatment-emergent abnormal values for serum creatinine or BUN at any time during the study. No SAEs were reported and no subject was discontinued from the

study due to an AE. Across both treatment regimens (5 days or 10 days), there was no apparent relationship between any safety parameter and exposure to peramivir. Peramivir exposure after the first dose was not different from that after either 5 or 10 days of twice-daily dosing, indicating no accumulation over these dose periods.

7.4.6 Immunogenicity

Peramivir is not a peptide; therefore, immunogenicity effects were not specifically evaluated during the clinical trials. As peramivir is a small molecule, it is highly unlikely to have a potential for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As noted throughout this review, no significant differences were noted between 300 mg and 600 mg peramivir doses with respect to safety. Risk differences between the two dose groups (per hundred) were consistently below 2% for all MedDRA SMQs (broad or narrow) and MedDRA Preferred Terms. Likewise, no dose dependency was seen in the analyses of vital signs, laboratory abnormalities, or ECGs. A thorough QTc study that employed a single dose of 1200 mg showed no evidence of effects on cardiac conduction or of increased frequency of adverse events with a supratherapeutic dose.

7.5.2 Time Dependency for Adverse Events

Time of Onset

Because peramivir was administered as a single dose in the clinical trials of acute uncomplicated influenza, time dependency analyses were not considered as relevant as they would be for chronically administered drugs. Most adverse reactions in the adult trials occurred early after treatment. Across all treatment groups, median time of AE onset was 3 days; mean time was 5 days in the peramivir and placebo groups and 4 days in the oseltamivir group.

TEAEs in the “Gastrointestinal Disorders” SOC tended to occur early and had a mean time of onset of 3 days in the peramivir groups. Mean time of onset for TEAEs in the “Investigations” SOC, which compromised the largest number of events, was 5 days. TEAEs with a more delayed time of onset (> 5 days after study drug administration) were generally in the “Infections and Infestations” or “Investigations” SOCs, or were observed in less 1% of subjects overall.

Time dependency analyses for the submission-specific events of interest, such as leukopenia/neutropenia, hepatic effects, renal events, rash, neuropsychiatric events, etc., are discussed in the individual subsections of Section 7.3.5.

Duration of Adverse Events

Median duration of TEAEs was comparable across treatment groups, ranging from 6 days in the oseltamivir group to 7 and 8 days in the PRV 300 mg and 600 mg groups, respectively, to 9 days in the placebo group. Mean duration times were 9-10 days for the peramivir and placebo groups and 7 days for the oseltamivir group. TEAEs lasting > 1 week tended to be in the "Investigations" SOC and were mostly not considered related to study drug; their incidence was also similar across treatment groups.

The most common TEAE associated with peramivir treatment was diarrhea. Mean duration of diarrhea was comparable between the peramivir groups (PRV 300 mg 2.4 days, PRV 600 mg 3.9 days) and control groups (3.3 days each for placebo and oseltamivir). However, six peramivir-treated subjects reported diarrhea lasting > 7days (PRV 300 mg 1, PRV 600 mg 5); mean duration was 14.5 days (range: 8-27 days). Five of the cases were mild and one was moderate; only one case (mild) required pharmacologic intervention. All six cases resolved by end of follow-up. In contrast, only one subject in the control groups (placebo) had diarrhea lasting > 7 days; this subject reported moderate diarrhea of 21 days duration.

7.5.3 Drug-Demographic Interactions

Given the lack of notable safety differences between the peramivir 300 mg and 600 mg doses, these two treatment groups were pooled together for the demographic subgroup safety analyses. The analyses by sex, race, and age were limited to common adverse events (i.e., occurring at an incidence ≥ 2%) that occurred at a greater rate on peramivir than placebo. Because these comparisons do not reflect randomization to the baseline characteristic of interest, these analyses are merely descriptive; no formal statistical comparisons were carried out.

Sex

As shown in Table 43, only four of the common AEs had a risk difference (per hundred) ≥ 2% between men and women: 'diarrhea' (relative risk [RR] women/men=1.1), 'neutrophil count decreased' (RR=1.87), 'white blood cells urine positive' (RR=3.07), and 'blood creatinine phosphokinase increased' (RR=0.19). The attributable risk of diarrhea due to peramivir was higher for women than men (1% and 0.2%, respectively), but not substantially so. Greater attributable risk was noted in women for neutropenia and pyuria and in men for CPK increases.

Table 43: Incidence of Common Adverse Events by Sex (Pooled Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Adverse Event	Number of Subjects (%)			
	Peramivir		Placebo	
	Male	Female	Male	Female

	(N=661)	(N=630)	(N=215)	(N=221)
Diarrhea *	44 (7)	55 (9)	14 (7)	17 (8)
Neutrophil count decreased *	27 (4)	48 (8)	0	0
Blood glucose increased	36 (5)	25 (4)	14 (7)	7 (3)
White blood cells urine positive *	2 (0.3)	37 (6)	1 (0.5)	7 (3)
Blood creatine phosphokinase increased *	17 (3)	3 (0.5)	1 (0.5)	1 (0.5)
Lymphocyte percentage increased	15 (2)	13 (2)	2 (1)	3 (1)
Blood phosphorus decreased	11 (2)	9 (1)	0	2 (1)
Dizziness	12 (2)	13 (2)	4 (2)	5 (2)

* Risk difference per hundred ≥ 2% between men and women in pooled peramivir group
Source: created by clinical reviewer using adverse event analysis dataset (ADAE.xpt) – Integrated Summary of Safety (ISS)

Because the reporting of AEs related to laboratory abnormalities was investigator-dependent and varied from trial to trial, particularly between the Shionogi and BioCryst trials, the laboratory data for CPK, urine WBCs, and neutrophils were reviewed to determine whether they correlated with the sex differences noted in AE reporting. In addition, the incidence rates of leukocyte and AST graded laboratory toxicities were analyzed by sex, as these parameters demonstrated a treatment effect between peramivir and placebo in the general population (Table 44).

Table 44: Incidence of Selected Laboratory Toxicities by Sex (Pooled Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Any Graded Toxicity	Number of Subjects (%)			
	Peramivir		Placebo	
	Male	Female	Male	Female
Creatinine Phosphokinase (U/L)	N=653 102 (16)	N=622 38 (6)	N=213 24 (11)	N=218 11 (5)
Leukocytes (10^3/μL)	N=651 26 (4)	N=623 57 (9)	N=211 3 (1)	N=219 6 (3)
Neutrophils (10^3/uL)	N=648 112 (17)	N=623 145 (23)	N=207 18 (9)	N=218 29 (13)
Aspartate Aminotransferase (U/L)	N=648 102 (16)	N=606 54 (9)	N=212 27 (13)	N=216 19 (9)
Urine leukocytes [a]	N=551 8 (2)	N=533 64 (12)	N=137 9 (7)	N=141 20 (14)

N = number of subjects with baseline laboratory values
a) N = number of subjects with baseline urinalysis without pyuria
Source: created by clinical reviewer using laboratory analysis dataset (ADLB.xpt) and analysis subject level dataset (ADSL.xpt) – Integrated Summary of Safety (ISS)

The results showed that while the risk ratios for graded increases in CPK were similar between men and women in the peramivir group (1.3 and 1.2, respectively) and the relative risk for men/women was 1.06 (i.e., no difference), the risk attributable to peramivir was greater in men than women (4.4% and 1.1%, respectively). Similar

observations were noted for AST elevations, where the relative risk for men compared to women was 1.21 but the attributable risk was 3% versus 0.1%, respectively. The reasons for these differences are not clear, but may be related to higher muscle mass in men and the role of IM peramivir in muscle toxicity events. Conversely, for leukopenia, the risk attributable to peramivir was higher in women than men (6.4% versus 2.6%); however, no such differences were noted for graded laboratory neutropenia. For pyuria, the overall incidence was less in the peramivir group than in the placebo group based on the laboratory data, suggesting that the effect was not due to peramivir therapy, regardless of sex.

Race

Table 45 displays the common TEAEs observed with peramivir by race, as well as TEAEs that occurred at a ≥ 2% greater incidence in one racial group over another. In general, no race differences were observed with respect to safety. It should be noted, however, that the majority of peramivir-treated subjects in the adult trials of acute uncomplicated influenza were Asian, thus limiting the generalizability of these comparisons. Nevertheless, TEAEs that were reported more frequently in one race over another within the peramivir cohort displayed similar trends within the placebo group, suggesting that the observed racial differences were probably not related to treatment. An argument could be made that White/Caucasian subjects were more at risk for vomiting and dizziness with peramivir therapy than Asians (RR=3 for each event), but the number of these events was small and the risk possibly attributable to peramivir was only 2% in each case. It is also interesting to note that certain hematological AEs, such as leukopenia and neutropenia, were only reported in Asians, reflecting either a possible true racial difference or the idiosyncrasies of Study 0815T0631, which contributed the bulk (> 700) of peramivir-treated Asian subjects. The TEAEs of 'CPK increased' and 'injection site pain' occurred predominantly in non-Asians and likely reflected the fact that BioCryst IM trials of peramivir were conducted exclusively outside of Asia.

Table 45: Incidence of Selected Adverse Events by Race (Pooled Peramivir 300 mg and 600 mg) - Controlled Trials in Acute Uncomplicated Influenza

Adverse Event	Number of Subjects (%)							
	Peramivir				Placebo			
	Asian N=950	White N=220	Black N=82	Other N=39	Asian N=124	White N=187	Black N=91	Other N=34
Diarrhea	84 (9)	10 (5)	3 (4)	2 (5)	17 (14)	11 (6)	3 (3)	0
Nausea	25 (3)	17 (8)	0	3 (8)	2 (2)	15 (8)	1 (1)	2 (6)
Vomiting	11 (1)	10 (5)	0	0	2 (2)	6 (3)	2 (2)	0
WBC decreased	25 (3)	0	0	0	5 (4)	1 (1)	1 (1)	0
Neutrophil count decreased	75 (8)	0	0	0	0	0	0	0

Blood glucose increased	59 (6)	2 (1)	0	0	18 (15)	1 (1)	0	2
ALT increased	31 (3)	4 (2)	0	0	8 (7)	2 (1)	1 (1)	2 (6)
Beta 2 microglobulin urine increased	22 (2)	0	0	0	11 (9)	0	0	0
WBCs urine positive	39 (4)	0	0	0	8 (7)	0	0	0
Proteinuria	0	5 (2)	0	2 (5)	0	5 (3)	1 (1)	2 (6)
Blood CPK increased	8 (1)	8 (4)	1 (1)	3 (7)	1 (1)	1 (1)	0	0
Lymphocyte percentage increased	28 (3)	0	0	0	5 (4)	0	0	0
Blood phosphorus decreased	20 (2)	0	0	0	2 (2)	0	0	0
Dizziness	15 (2)	8 (4)	1 (1)	1 (3)	4 (3)	4 (2)	1 (1)	0
Injection site pain	1 (<1)	6 (3)	1 (1)	1 (3)	1 (1)	2 (1)	1 (1)	0
Chest pain	3 (<1)	1 (1)	2 (2)	0	0	0	1 (1)	0

Not unexpectedly, safety analyses by country or region produced similar findings as those above. Formal analysis by ethnicity was not done given the small number of Hispanic subjects treated with peramivir in these trials: 22 overall, 13 (1%) at the 300 mg or 600 mg dose (see Table 6).

Age

In the five controlled adult trials of peramivir in acute uncomplicated influenza, 98% of subjects were between the ages of 18 and 65 years. In Study 0722T0621, this was in accordance with the protocol, but the remaining four protocols did not specify an upper age limit yet enrolled few elderly subjects.

Among subjects treated with peramivir 300 mg or 600 mg, only 24 (1.9%) were ≥ 65 years of age; in the placebo group, there were only 2 such subjects. Thus, risk analyses by age < or ≥ 65 years were of limited value. In the peramivir cohort, TEAEs that occurred in more than 1 subject aged ≥ 65 years included: 'blood glucose increased', 'nausea', 'white blood cells urine positive', 'chest pain', and 'neutrophil count decreased'. These events occurred in only 2 subjects (8%) each.

This reviewer conducted a categorical analysis of safety based on age < or ≥ 45 years; this age cut-off was arbitrarily chosen to distinguish younger subjects from middle-aged subjects. No risk difference ≥ 2% was noted in the peramivir group between these two age groups for any TEAE. Nausea, vomiting and abdominal pain tended to occur more frequently among subjects ≥ 45 years of age compared with younger subjects, but the differences were relatively small (risk differences per hundred: 1.3% -1.7%).

The Phase 1 trials had 39 subjects aged ≥ 65 years treated with either single or multiple doses of peramivir. Among these subjects, 54% experienced TEAEs, most of which were mild in severity. The most commonly observed TEAE in this age group was diarrhea (15%). Please refer to Section 7.4.5 for description of the dedicated Phase 1 safety study in healthy elderly subjects (Study BXC1812-104).

The clinical trials in hospitalized influenza patients had greater representation of peramivir-treated subjects who were ≥ 65 years old (14-24%); these subjects accounted for approximately 7% of the total subject population who received peramivir across the pooled Phase 2/3 trials. In the controlled hospital trials, the overall incidence of TEAEs increased with age in both the peramivir and placebo treatment groups. Among peramivir-treated subjects, a higher incidence of TEAEs considered related to study drug was observed in subjects aged ≥ 75 years (18%) compared to subjects aged 65-75 years (9%), but this was also seen with placebo. In the non-controlled hospital trial Study BCX1812-303, subjects aged 65-75 years experienced the highest incidence of TEAEs (88% in the < 300 mg peramivir group and 100% in the ≥ 600 mg peramivir group). In general, geriatric subjects in the < 300 mg peramivir group experienced a higher incidence of life-threatening AEs than those in the ≥ 600 mg peramivir group; however, subjects in the < 300 mg group had greater baseline disease severity due to the inclusion of subjects with severe renal dysfunction. While the trials in seriously ill hospitalized influenza patients showed higher rates of TEAEs in elderly subjects treated with peramivir compared to younger subjects, these findings might have also reflected the greater morbidity associated with influenza in the elderly and the greater comorbidity and greater number of concomitant medications frequently seen in this population.

Please refer to Section 7.6.3 for a review of peramivir safety in pediatrics.

7.5.4 Drug-Disease Interactions

Renal Dysfunction

In the adult clinical trials in acute uncomplicated influenza, 97% of subjects had normal to mildly impaired renal function, defined as estimated creatinine clearance (eCrCl) ≥ 60 mL/min by the Cockcroft-Gault formula. Among peramivir-treated subjects, 37 subjects had moderate renal impairment (35 treated with PRV 300 mg or 600 mg), defined as eCrCl ≥ 30 to < 60; and only one subject was enrolled with severe renal impairment, defined as eCrCl < 30 (treated with IM PRV 600 mg).

Within the pooled PRV 300 mg and 600 mg group, subjects with moderate to severe renal impairment had a higher overall incidence of TEAEs (58%) compared to subjects with normal or mildly impaired renal function (50%) and they had more Grade 2-3 events; however, similar patterns were observed among oseltamivir-treated subjects as well. TEAEs that occurred in more than 1 subject with moderate to severe renal impairment and at a greater incidence (≥ 2% risk difference) compared with subjects

with normal-mild renal function were all laboratory abnormalities, including 'blood glucose increased' (8% versus 5%), 'blood phosphorus decreased' (6% versus 1%) and 'protein urine present' (11% versus 4%). These findings should be interpreted with caution given the small sample size, small number of events, and possible underlying comorbidities associated with renal impairment. Nevertheless, other than ''blood glucose increased' and 'blood phosphorus decreased', the incidence of common AEs associated with peramivir (Table 39) was comparable between subjects with moderate to severe renal impairment and those with normal or mild renal impairment.

Please refer to Section 7.4.5, 'Renal Impairment Study' for a discussion of safety in the Phase 1 open-label Study BCX1812-105 in adults with renal impairment.

Hepatic Dysfunction

Specific studies of peramivir in subjects with hepatic dysfunction have not been conducted, but it is known that peramivir is not metabolized by the liver. With the exception of Study BCX1812-303, which had broad eligibility criteria and allowed entry of subjects with ALT and AST up to 5x ULN and bilirubin up to 6 mg/dL, the peramivir clinical trials excluded subjects with significant liver disease.

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review by Dr. Leslie Chinn for discussion of drug-drug interactions with peramivir. Key drug interactions with respect to safety are outlined below.

Peramivir with Oseltamivir

Study BCX1812-109 was a Phase 1 open-label, randomized, 3-period, 3-sequence crossover drug interaction study of peramivir and oseltamivir in healthy adult volunteers (N=21). Following IV administration of 600 mg peramivir in combination with oral oseltamivir (75 mg), the PK parameters for peramivir and oseltamivir carboxylate, the active moiety, showed no evidence of a drug interaction. The study medications (oseltamivir and peramivir taken individually or together) were generally well tolerated. The most common TEAE reported was headache, reported by 2 subjects (10%) in each cohort. All TEAEs were mild. The most common TEAEs considered by the investigator to be possibly, probably, or likely related to the study drugs were headache, dizziness, and influenza-like illness. No deaths or other SAEs were reported and no subjects withdrew from the study due to TEAEs. No substantial differences in clinical chemistry, hematology, or urinalyses values were noted between study sequences or from Baseline to Day 2 visits. The highest graded post baseline laboratory shifts were all Grade 1.

Peramivir with Rimantadine

Study BCX1812-108 was a Phase 1 open-label, randomized,3-period, 3-sequence crossover study to evaluate the effects of single-dose 100 mg oral rimantadine tablets on the PK of a single IV dose of peramivir (600 mg) and vice versa in healthy adult subjects (N=21). Results of this trial suggested that concomitant treatment with rimantadine and peramivir would not result in a PK drug interaction between the two drugs. The study drugs were generally well tolerated. The most common TEAE was headache, reported by 2 (10%) subjects who received rimantadine and peramivir and 1 (5%) subject each who received rimantadine or peramivir alone. All TEAEs were mild. Headache, dizziness, nausea, and chest pain were considered by the investigator to be possibly, probably, or definitely related to peramivir or rimantadine. No deaths or other SAEs were reported. One subject (who received rimantadine plus peramivir treatment) discontinued from the study due to a mild TEAE of viral gastroenteritis. The highest graded treatment-emergent laboratory shift was a Grade 2 low phosphorus level (2.2 mg/dL, normal range 2.5-5.0 mg/dL); all other laboratory values were Grade 0 or Grade 1. No substantial differences in clinical chemistry, hematology, or urinalysis values were noted between study sequences or from Baseline to Day 2 visits.

Peramivir with Probenecid

Study BCX1812-111 evaluated the PK parameters, safety, and tolerability of a single dose of 1 g oral probenecid coadministered with 1 of 3 doses of peramivir IM or IV. In a population of healthy males and females 19 to 57 years of age (N=27), peramivir in single doses of 75 mg, 150 mg, or 300 mg administered IM (with or without oral probenecid) or IV was generally safe and well tolerated; peramivir exposure was not affected by concomitant administration of probenecid. The most common TEAE was elevated CPK, which was observed only after IM injection of peramivir; the incidence was 6% in subjects who received 150 mg IM and 71% in subjects who received 300 mg IM. With the exception of increased CPK, there was no other event for which a dose relationship was apparent. Other TEAEs that occurred in more than 1 subject per treatment were headache (8% IV, 12% IM) and dizziness (4% IV, 6% IM). All TEAEs were either mild (93%) or moderate (7%) in severity. There were no SAEs reported and no subjects withdrew participation due to a TEAE.

Peramivir with Oral Contraceptives

Study BCX1812-110 was a Phase 1 blinded, randomized, placebo-controlled, 2-period crossover drug interaction study to evaluate the safety and PK parameters of ethinyl estradiol/levonorgestrel alone compared with co-administration with a single dose of IV peramivir 600 mg in healthy female volunteers (N=34). There were no PK or drug-drug interactions observed following coadministration of oral contraceptives and IV peramivir under fasted conditions in this study. Adverse events were generally mild and similar across treatment groups. In subjects receiving peramivir and ethinyl

estradiol/levonorgestrel, 25% experienced at least 1 TEAE, whereas 29% of subjects receiving placebo and ethinyl estradiol/levonorgestrel experienced at least 1 TEAE. The most common TEAEs were headache and nausea. No SAEs or events of significance were reported, and no subjects withdrew from the study due to a TEAE.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Peramivir was not mutagenic or clastogenic in a battery of genotoxicity studies nor carcinogenic in a rat oral carcinogenicity study; the latter was reviewed by the FDA Executive Carcinogenicity Assessment Committee (CAC). Please refer to the Pharmacology-Toxicology review by Dr. Kuei-Meng Wu for details.

The dosage of peramivir proposed for the acute uncomplicated influenza indication is a one-time single dose. As such, the potential for human carcinogenicity seems low. Across the six trials of peramivir in adults with acute uncomplicated influenza, only one subject had an event reported under the Neoplasms SOC:

- **Subject BCX1812-211.028.008** was a 55-year-old African-American woman treated with 300 mg IM peramivir and reported to have a nonserious Grade 1 soft-tissue mass in her right upper buttock (PT: 'soft tissue neoplasm') on Study Day 12 that was considered possibly related to study drug by the investigator. The event was considered resolved on Day 58.

  Medical Officer's comment: it is possible that the soft-tissue mass reported in this subject was related to the gluteal IM injection of peramivir; however, there was insufficient information in the subject's CRF to make that determination.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy

There are no adequate and well controlled clinical trials of peramivir use in pregnancy. As described in Section 4.3, animal data in rats demonstrated that peramivir at doses of up to 600 mg/kg did not produce maternal toxicity or embryotoxicity.

Pregnancy was an exclusion criterion in the clinical trials of peramivir in acute uncomplicated influenza. Nonetheless, two pregnancies occurred in these trials, one in Study BCX1812-211 (Subject 461-001) and one in Study BCX1812-212 (Subject 107-002). Both subjects were treated with peramivir 300 mg IM and both pregnancies were terminated electively. There were no suspected fetal anomalies.

When the 2009-2010 H1N1 influenza pandemic highlighted the potential for severe disease in pregnant women, the protocol for Study BCX1812-301 allowed pregnant women to enroll, with enhanced follow-up through the end of the pregnancy up to the child's first birthday to ascertain pregnancy outcomes and infant outcomes. Two pregnancies were reported in this trial; one was nonviable due to a benign hydatiform mole and the other was terminated electively for personal reasons. There were no suspected fetal anomalies. There was one other pregnancy in BCX1812-301 that resulted in a healthy infant, but that subject was treated with placebo.

Scant pregnancy information was available from the EUA and eIND experience. Since there were no patient identifiers under the EUA, no follow-up could be attempted; however, limited information regarding four pregnancies was provided:

- One 27-year-old woman who received EUA peramivir contacted BioCryst and voluntarily provided information on her clinical course and pregnancy outcome, which was delivery of healthy infant at term.
- Another woman of unknown age with renal failure and ARDS from presumed influenza virus infection delivered a healthy baby on the second day of peramivir administration.
- A third woman, age 22, was administered peramivir 600mg IV daily via the EUA and 6 days after completion of peramivir therapy, experienced a spontaneous abortion (further details not provided).
- A fourth woman, age 33, was treated with 600 mg daily of peramivir for 10 days via the EUA. The patient experienced delirium and myopathy during the pregnancy. Outcome of the pregnancy was not reported.

Minimal information is known about subjects who received peramivir via eIND, but follow-up was obtained for two pregnant subjects, ages 22 and 23, indicating healthy infant outcomes.

Lastly, there were six reports of pregnancy in the postmarketing setting, one of which occurred in Shionogi's observational postmarketing surveillance study. All the events occurred in Japan. Healthy pregnancy outcomes were known for three of the cases and outcomes were unknown for the other three. There have been no reports of any anomalies or pregnancy complications thus far in patients who have received peramivir.

In conclusion, although clinical data regarding the use of peramivir in pregnancy are limited, animal studies suggest that the possibility of fetal harm in humans is remote. Further, limited non-controlled data from the EUA, eIND, and postmarketing experience have not demonstrated any untoward effects of peramivir on pregnancy outcomes. Given the increased risk of severe influenza in pregnancy, peramivir use may be considered in pregnancy if clearly needed and if the potential benefit outweighs any potential risk.

(b) (4)

the FDA review team has determined that Category C (b) (4) appropriate. The other

two drugs in the NAI class are also Pregnancy Category C. Please refer to the Pharmacology-Toxicology review by Dr. Kuei-Meng Wu for further discussion of the pregnancy category determination for peramivir.

Breastfeeding

Studies of peramivir in rats demonstrated that peramivir is excreted into breast milk at levels below the mother's plasma drug concentration. Although it is not known if peramivir is excreted into human breast milk, peramivir has been used safely in a small number of infants less than 1 year of age (Study 098T0633, see Section 7.6.3). Also, while there have been no clinical studies directly analyzing peramivir use in lactating women, two nursing mothers were successfully treated with peramivir in the Japanese observational postmarketing surveillance study. Nonetheless, given the lack of controlled clinical data, caution is advised if peramivir is to be administered to a nursing mother.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric Trials in Acute Uncomplicated Influenza

Study 0918T0633 was a Phase 3 multicenter, non-controlled open-labelled trial conducted in Japan during the fall of 2009. The safety, efficacy, and PK of peramivir at 10 mg/kg (up to a maximum of 600 mg) were evaluated in pediatric subjects 28 days to < 16 years of age with influenza A or B infection. Subjects with positive RAT were enrolled within 48 hours of onset of influenza symptoms and could be treated for up to 5 days based on the persistence of elevations in body temperature ≥ 38.0°C and clinical signs or symptoms. A total of 117 subjects were enrolled at 35 study sites in Japan and treated with peramivir (safety population); 115 subjects were in the ITTI and PK population.

Clinical efficacy evaluations included subject self- or proxy consenter-assessments of body temperature, severity of influenza symptoms, and evaluation of usual activities, recorded daily in a patient diary from screening until Day 14. Body temperature was taken 4 times a day from screening until Day 3 and twice a day from Days 4 to 14. Severity of influenza symptoms was assessed twice daily, and activities of daily living once daily. Other efficacy assessments included viral titer ($TCID_{50}$/mL), NA-inhibitory activity (IC_{50}), CRP determination, and assessment of influenza-related complications. Subjects could be inpatient or outpatient. The primary endpoint in this trial was time to alleviation of symptoms (cough and nasal discharge) and body temperature < 37.5°C; this endpoint was different than that used in earlier pediatric trials of acute influenza and was not a validated endpoint.

Most subjects (107 [91%]) received IV peramivir for 1 day, while 10 (9%) subjects received IV peramivir for 2 days. Fifty-one percent of subjects were male and all were outpatient. Mean age was 8.9 years. There were five age brackets:

- 28 days to < 1 year, n = 4 (4%)
- 1 to < 2 years, n = 8 (7%)
- 2 to < 6 years, n = 20 (17%)
- 6 to < 12 years, n = 46 (40%)
- 12 to < 16 years, n = 37 (32%)

The mean influenza score was 1.6 points for cough and 1.4 points for nasal discharge (based on a 4-point scale). Two subjects were excluded from the ITTI population because they lacked clinical efficacy data. Of the remaining 115 subjects, all were positive for influenza A on RAT. Typing of influenza was possible in 107 subjects and all were found to have influenza A; of these, 106 subjects had influenza A/H1N1pdm09 and one subject had unknown subtype.

In the ITTI population, the median TTAS was 27.9 hours (95% CI 21.7-31.7 hours). The median TTAS ranged from 25.6 hours to 31 hours for the consecutive age brackets, and were comparable between age groups. The median time to recovery to temperature < 37.5°C was 20.4 hours (95% CI: 19.1-20.9). The median times to recovery to normal temperature for consecutive age brackets were comparable, ranging from 19.7 to 20.8 hours. The percentage of influenza virus-positive subjects decreased from 78% on Day 2 to 7% on Day 6.

Per the Applicant, PK results indicated that plasma concentrations in pediatric subjects were within the range observed following administration of peramivir at 300 or 600 mg in adults with acute uncomplicated influenza

Of the 117 subjects in the safety population, 73 (62%) experienced 116 TEAEs. Most TEAEs were mild or moderate and occurred mostly on Day 2 to Day 3. The overall incidence of TEAEs was highest in subjects aged ≥ 28 days to < 1 year (75%) and lowest in subjects aged ≥ 12 to < 16 years (54%); TEAE incidence did not differ between subjects receiving one or two doses of peramivir (63% and 60%, respectively). No deaths occurred. SAEs were reported in 2 subjects: ‘influenza pneumonia’ in one subject and ‘pneumonia’ and ‘encephalopathy’ in another subject. Both subjects discontinued from study but recovered. No other subject discontinued from the study due to AEs. The most frequent TEAEs by PT were ‘neutrophil count decreased’ (21%, 25 subjects), ‘diarrhoea’ (16%, 19 subjects), and ‘eosinophil count increased’ (8%, 9 subjects). In most cases of diarrhea, the event was mild and followed by a quick recovery. There were 13 non-serious severe events: 10 events of ‘neutrophil count decreased’ and 1 event each of ‘blood urine present’, ‘urine ketone body present’, and ‘CK increased’. All events were documented as recovered except for a ‘neutrophil count decrease’ that was not followed to recovery since it was deemed unrelated to peramivir use. Five of the 19 subjects with ‘neutrophil count decreased’ entered the trial with low

neutrophil counts at baseline. There were no TEAEs related to blood pressure or other vital signs, nor were there any changes of clinical concern in these parameters.

With respect to AEs of interest, 'ALT increased', 'AST increased', 'CK increased', and proteinuria were reported in 1 (0.9%) subject each. The case of proteinuria was judged to be related to the underlying illness; no other renal-related AEs were reported. Six (5%) subjects had AEs in the "Skin and Subcutaneous Tissue Disorders" SOC, but most of these were dermatitis, eczema or heat rash; only 1 (0.9%) subject had 'rash' reported.

Three (3%) subjects had TEAEs of 'abnormal behaviour'. These events occurred 1 each in the three age brackets that were ≥ 2 years of age. In two of these cases, the events were not considered related to study drug but rather were seen at the time of onset of influenza or high fever; in the third case, a causal relationship to peramivir could not be ruled out. All cases of 'abnormal behaviour' were mild in severity and quickly recovered. In addition, as noted above, an SAE of 'encephalopathy', accompanied by 'pneumonia', was also reported in another subject. This subject, a 5-year-old boy, also experienced convulsion; however, all of these events were considered related to the influenza illness rather than study drug (refer to Section 7.3.5 "Seizures" for further details of this case).

Although no placebo control was utilized in this trial, the safety profile of peramivir in pediatrics was similar to that observed in adults with acute uncomplicated influenza.

Clinical Trials in Hospitalized Patients

Two children and 11 adolescents were enrolled in Studies BCX1812-301 and -303.

In BCX1812-301, three adolescents were enrolled in the peramivir 5 mg/kg bid arm and one in the 10 mg/kg daily arm. Only one subject tested positive for influenza and all but one received an NAI in addition to peramivir. One 14-year-old girl with confirmed H1N1 influenza in the 5 mg/kg bid arm experienced a skin lesion on her nose and decreased temperature. Another 14-year-old girl who tested negative for influenza in the 5 mg/kg bid arm experienced decreased consciousness. This subject enrolled with septic shock at baseline and was heavily sedated due to her critical condition. Her parents withdrew consent for the study after two doses (24 hours) of peramivir. The other two subjects had no AEs reported.

In BCX1812-303, there were very few AEs reported among the small number of enrolled pediatric subjects.

- Two children and seven adolescents were enrolled in the peramivir plus SOC arm; all received a NAI-containing regimen as SOC. One 17-year-old boy had phlebitis and one 16-year-old boy had nausea, gastritis, cystitis and laryngitis; the other seven subjects had no AEs reported.

- Two children and four adolescents were enrolled in the placebo plus SOC arm; all but two received an NAI-containing SOC regimen. One 16-year-old boy had two AEs of 'alanine aminotransferase increased' and 'aspartate aminotransferase increased', another 16-year-old boy had 'diarrhoea' and 'headache', and a 9-year-old boy had erythema of the ear.

In summary, IV peramivir appeared to have an acceptable safety profile in the small number of pediatric subjects enrolled in these hospitalized trials. However, interpretability of the safety data was confounded by concurrent severe illness and limited by the small sample size and small number of events.

Emergency Use Authorization and Emergency IND Use

The FDA publication regarding the 2009 EUA experience with peramivir (Sorbello et al, 2012) included information on 28 children, the youngest being 3 years of age. Of these, 16 children died; however, no deaths were attributed to peramivir by the treating physicians. These patients were severely ill; many had mechanical ventilation and extra corporeal membrane oxygenation (ECMO) reported as concomitant therapies. The most commonly reported AEs by Preferred Term in children and adolescents were 'death' and 'respiratory failure', with three reports each. In addition, there were multiple events representing renal failure, vascular instability (e.g. 'hypotension', 'vascular insufficiency', 'shock'), and neurologic disorders (e.g. 'paralysis', 'hypotonia', 'polyneuropathy').

Under eIND regulations, peramivir was administered to 11 critically ill subjects under the age of 18 years; three were < 9 years old and eight were 10 years or older. Pediatric subjects were treated with 10 mg/kg peramivir daily and some received 600 mg; there were two subjects with renal failure undergoing continuous hemofiltration who received reduced doses of peramivir. All of the treated subjects had pneumonia with respiratory failure requiring mechanical ventilation. Four of the subjects died, but six recovered and one was transferred to another hospital for a heart transplant.

In summary, interpretability of the EUA and eIND data is limited by the severity of disease in children who received peramivir and the uncontrolled nature of the data.

Postmarketing Experience

1) Observational Surveillance Study

A total of 1,254 patients < 15 years of age were evaluated at 173 institutions in Japan, in a routine pediatric setting, as part of a post-approval observational safety and efficacy surveillance study conducted by Shionogi between October 2010 and February 2012. The evaluable safety population was 1,199 following the exclusion of 50 patients who were never observed after the start of treatment, one patient who was treated outside the investigation period, and four duplicate cases. (No AEs occurred in the patients

excluded from safety analysis.) Approximately half of the patients were ≥ 1 to < 7 years of age, and 4.5% were < 1 year of age, including one patient who was < 4 weeks of age. Fifty-five percent of the population was male. Almost all patients (84%) received peramivir within 1 day of the start of influenza symptoms. Most patients were treated in an outpatient setting, but 138 (11.5%) were hospitalized for influenza, and 11 had serious influenza, defined as either influenza encephalopathy or the need for mechanical ventilation. Almost all patients (97%) received only 1 day of peramivir.

A total of 92 patients experienced 115 AEs deemed related to peramivir by the prescribing physicians; 14 of the AEs were serious. There were five SAEs of abnormal behavior and five SAEs of neutropenia (two severe). There were no fatal AEs reported. Most of the AEs (87%) occurred within 3 days after the start of treatment with peramivir, and almost all (94%) of the AEs recovered or improved. Durations of AEs were brief, with 81% resolving or improving within 3 days of onset.

The most common AEs were 'diarrhoea' (30 events, 3%), 'abnormal behavior' (27 event, 2%), 'vomiting' (8 events, 0.7%), and 'nausea' (8 events, 0.7%). There were no noticeable differences in AE incidence between the various pediatric age groups. The sole enrolled neonate (< 4 weeks of age) did not experience any AEs. Patients aged ≥ 4 weeks to < 1 year had a 9% incidence of AEs; those ≥ 1 to < 7 years of age had a 7% incidence of AEs; and children ≥ 7 to < 15 years of age had an 8% incidence of AEs. No new safety signals were detected in this post approval surveillance study. Abnormal behavior and neutrophil count decreased were events of interest and are discussed further here:

- *Abnormal behavior*
  In this study, 27 patients reported 31 events of abnormal behavior, of which five were SAEs. In 3 of the 5 patients with SAEs, there was a complication of influenza encephalopathy or febrile convulsion preceding the event. Descriptions of abnormal behavior varied greatly. Temperatures at the time of the AE ranged from 37º to 41ºC, with a median of 38.8ºC; temperature was unknown in four instances. In some cases, duration of the abnormal behavior was only a few minutes; the range was 5 minutes to 4 days. Nineteen AEs resolved within a few minutes to 1 hour of onset, seven AEs lasted 2-4 hours, and two AEs lasted 10 hours. One AE lasted 4 days in a 3 year-old boy, but he was in an induced coma for influenza encephalopathy and underwent hypothermia therapy; the description of the event indicated that he did not wake from the thiopental-induced coma easily, required mechanical ventilation after spontaneous respirations began, and continued to have eye rolling and dyskinesia. Duration was unknown in one event.

- *Neutrophil count decreased*
  There were five SAEs and one nonserious AE. All of the patients with SAEs had complications of influenza such as bacterial infections or encephalitis. In two of the cases, the neutrophil count decreased below 500 cells/μL. In the first case, a 9-year-old boy with cerebral palsy, chronic respiratory disorder, epilepsy, and eating and swallowing disorders received 3 days of peramivir; his neutrophil count reached a nadir

of 312 cells/μL three days after administration was completed. The event resolved without treatment after 9 days. The second case was a 6-year-old girl who had bronchitis treated with ceftriaxone at baseline. Her neutrophil count decreased to 1600 cells/ μL the day after her 1 dose of peramivir. Because she continued to have fever, peramivir was administered again 2 days later and her neutrophil count decreased to 424 cells/μL. The outcome was unknown. In the three other SAEs, the nadir ranged from 855 to 952 cells/μL; all events resolved without treatment.

2) Spontaneous Postmarketing Safety Reports

Among spontaneous postmarketing AEs reported to Shionogi, non-serious AEs were reported for 67 pediatric patients; the most commonly reported non-serious AEs were in the Psychiatric Disorders SOC, primarily abnormal behavior. In addition, rash, diarrhoea, and urticaria were commonly reported in pediatrics. These events were consistent with AEs reported in the pediatric Study 0918T0633 and the pediatric post-approval surveillance study noted above.

Non-serious events reported in postmarketing that were not seen during clinical development included speech disorder (2 events), palpitations (3 events), and angiopathy (3 events). These are described here:

- *Speech disorder*
  - One event of speech disorder occurred in a 9-year-old boy who had a fever. The event was described as “delirious words”, making this more consistent with delirium brought on by fever; the patient recovered.
  - The second case was reported in the literature as occurring in a 9-year-old boy with an unknown recovery; the reported information was too minimal to interpret.

- *Palpitations*
  - The three AEs of palpitations were reported as symptomatology only, with no documented arrhythmia or tachycardia, and appeared consistent with underlying influenza, fever, and/or dehydration.

- *Angiopathy*
  - Angiopathy was described as vascular pain and occurred in one 9-year-old and two 10-year-old patients; however, it is difficult to determine if peramivir played any role in these events or if they were due to difficult IV needle placement.

Serious AEs were reported for 17 pediatric patients. Most SAEs reported in the postmarketing setting were also observed during clinical development. The most commonly reported SAEs in children were abnormal behavior (4 events) and anaphylactic shock (2 events). The events of anaphylactic shock did not meet clinical criteria as true anaphylaxis and likely represented vasovagal reactions. They are described here:

- A 14- year old boy felt queasy after 3 minutes of peramivir infusion. His systolic blood pressure was 68 mmHg. He was treated with IV fluids and steroids and recovered in 7 minutes with a normal blood pressure.
- A 16-year-old boy had a cold sweat and felt queasy within 20 seconds of starting his infusion. His blood pressure was decreased. The infusion was stopped and he was treated with IV steroids with recovery.

Significant SAEs not reported during clinical development included convulsion (2 events), nephritis (1 event), metabolic acidosis (1 event) and pubis fracture (1 event). The two events of convulsion are described in Section 7.3.5 “Seizures”. The other events are described here:

- *Nephritis*
  The event of nephritis occurred in a 9-year-old girl who developed fever and diarrhea. She was found to have hemolytic streptococcal infection and therapy with meropenem and tosufloxacin was initiated. Her fever persisted to 40°C and she returned to the hospital, where influenza was diagnosed. She received a dose of peramivir and was admitted. She improved and was discharged (b) (6) days later. Four days after peramivir, she developed a suspected drug-induced nephritis and received fosfomycin. This case was confounded by concurrent illness and other medication use.

- *Metabolic acidosis*
  The event of metabolic acidosis occurred in an 8-year-old boy in the context of pneumococcal sepsis.

- *Pubis fracture*
  The event of pubis fracture occurred in an 8-year-old boy who was diagnosed with influenza and treated with peramivir. He was febrile for 1 day and then improved. Two days after peramivir infusion, he jumped out of the second story of his home and fractured his pubis. He had no memory of the event.

In summary, no AEs (serious or non-serious) were reported in the postmarketing setting that represented significant new safety risks in pediatrics. Neuropsychiatric changes are described with other NAIs, although underlying influenza may be a contributing factor.

Pediatric Study Plan

A single clinical trial to evaluate the efficacy, safety, and PK of IV peramivir in U.S. pediatric subjects from birth to 18 years of age is planned to initiate during the 2014/2015 influenza season. The to-be-marketed formulation will be used in the pediatric trial.

A protocol synopsis of the proposed pediatric trial was submitted with this application; it

(b) (4)

The Applicant requests deferral of the proposed pediatric trial until after NDA approval in adults.

Medical Officer's Comment:
On August 13, 2014, the clinical review team presented the Applicant's Pediatric Study Plan to the FDA Pediatric Review Committee (PeRC). The study design of the pediatric trial was discussed in particular, (b) (4) *is considered inadequate to evaluate either safety or efficacy of peramivir in a pediatric population. The PeRC opined that a partial extrapolation of efficacy appeared to be the*

most reasonable approach and that an active-controlled trial to evaluate the safety of peramivir in comparison to other approved products (e.g. oseltamivir) would be reasonable. The review team concurred and also recommended that the pediatric trial not enroll hospitalized subjects as this would not fit the proposed indication and combining safety assessments from ambulatory and hospitalized cohorts would complicate interpretability. Further recommendations regarding sample size and age-appropriate assessments will be made to the Applicant. The PeRC agreed with the deferral request.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Overdose with peramivir has not occurred; thus, there has been no experience with overdose. Single doses of peramivir up to 1200 mg/day, representing a 2-fold increase above the planned dose, have been well tolerated (see Section 7.4.5 “Thorough QT Study”). As peramivir will be administered under supervised conditions by health care providers, overdose is not anticipated.

Drug Abuse Potential

Peramivir has no known potential to result in abuse or dependence. In animal models, peramivir does not cross the blood-brain barrier, making it unlikely to be a potential drug of abuse. Further, it is not anticipated that there will be any effects on the ability to drive or operate machinery due to peramivir administration.

Withdrawal and Rebound

Effects of withdrawal and rebound with use of peramivir were not assessed. No such effects are anticipated given the conditions under which the product will be used.

7.7 Additional Submissions / Safety Issues

On October 23, 2009, the FDA issued an EUA for IV peramivir to treat suspected or confirmed cases of influenza A/H1N1pdm09 virus infection in hospitalized patients who were unresponsive to or unable to tolerate available antivirals or lacked dependable oral or inhaled drug delivery routes. From October 23, 2009 to June 23, 2010, the CDC delivered 2,129 five-day adult treatment course equivalents of peramivir to 563 hospitals. Based on data requests made to treating physicians, approximately 1,274 hospitalized patients received peramivir through the EUA program. The EUA required healthcare providers to report medication errors, selected AE, SAEs, and deaths to the FDA. Reviewers from the FDA Office of Surveillance and Epidemiology (OSE) and DAVP analyzed reports submitted to the Adverse Event Reporting System (AERS) and sought follow-up in selected cases.

The FDA received AERS reports for 344 patients (including 28 children and 3 pregnant women).[12] Many patients were critically ill on mechanical ventilation (41%) and renal replacement therapies (19%); 38% had received oseltamivir. The most frequently reported SAEs by MedDRA Preferred Term were death (15%), H1N1 influenza (8%), respiratory failure (8%), acute renal failure (7%), and ARDS (7%). Six medication errors were reported. A total of 206 deaths were reported to the FDA, including 53 patients (15% of the total study population) with an outcome of death coded as an AE. None of the deaths were attributed to peramivir by the reporting physician, and most deaths occurred among patients who were obese, immunosuppressed, or aged > 65 years; most had received oseltamivir. Rash was the only TEAE attributable to peramivir. Influenza severity, comorbidities, and concomitant medications confounded additional safety assessments. Missing clinical and laboratory data further precluded evaluation of some reports. The FDA review team concluded that the safety data were insufficient to assess whether peramivir affected outcome or caused adverse reactions other than rash. (Pregnancies that occurred under the EUA are discussed in Section 7.6.2.)

8 Postmarket Experience

As noted in Section 2.6, IV peramivir was approved in Japan in January, 2010. Shionogi collects spontaneous AEs reported in Japan and Taiwan. Data from marketing approval to the data cut-off September 30, 2013 were reviewed by the Applicant for this NDA. It is estimated that (b) (4) Japanese patients have been exposed to commercial peramivir during this reporting period. A total of 407 spontaneous AEs were reported in 324 patients (adults and pediatrics), of which 265 events were considered non-serious, and 140 events were considered serious. The pediatric postmarketing experience is discussed in Section 7.6.3; this section will focus on the postmarketing experience reported in adults.

Nonserious Spontaneous Adverse Events

Non-serious AES were reported for 126 adult patients (18-94 years) and 20 patients of unreported age. The most common AEs reported were gastrointestinal, including diarrhoea, vomiting, and nausea. This was consistent with the TEAEs reported in clinical development and post-approval surveillance studies. In addition, rash, urticaria, dizziness, and hallucinations were also commonly reported.

Almost all of the nonserious events reported in postmarketing were seen during clinical development in subjects with acute uncomplicated influenza with the exception of certain events in the Nervous System Disorders SOC (‘altered state of consciousness’ [2 events] and ‘loss of consciousness’ [3 events]), and in the Psychiatric Disorders SOC (‘abnormal behaviour’ [4 events], ‘delirium’ [4 events] and ‘hallucinations’ [6 events]).

Delirium was reported in hospitalized subjects with influenza. The 14 events of abnormal behaviour, delirium, and hallucinations reported in 13 patients were consistent with events reported in postmarketing for other NAIs. Nine of the 13 patients were ≥ 75 years old, and all had improved or recovered from the events. The remaining cases were either consistent with vasovagal reactions or contained scant information, but all seemed to recover. In addition, these patients had influenza which can result in high fever and delirium.

Serious Spontaneous Adverse Events

Serious AEs were reported for 94 adult patients, 10 of which were of unreported age and 1 was an unknown age in the 10th decade of life. The most commonly reported SAEs were 'hepatic function abnormal', 'shock', and 'anaphylactic shock' with 6 reports each. In addition, there were 5 reports of 'enterocolitis haemorrhagic' and 4 reports of 'liver disorder' and 'acute renal failure'. The frequency of reports resulted in hepatic toxicity, shock, anaphylaxis, and haemorrhagic colitis becoming events of special interest that informed the safety review of peramivir for this NDA.

Most events reported in the postmarketing setting were seen during development. Significant SAEs not previously reported during clinical development included sudden death (2 events), torsade de pointe (1 event), and convulsion (1 event). The two cases of sudden death and the one case of convulsion were briefly discussed in Section 7.3.1 and Section 7.3.5 "Seizures", respectively, but all are described in further detail here:

- *Sudden Death*
  - A 50-year-old man developed influenza and received oseltamivir. He continued to deteriorate and was admitted to the hospital, where he received 1 dose of peramivir. During this time, he developed severe weakness with CPK levels > 16,000 IU/L. He was started on antibiotics for presumed pneumonia. The patient experienced a sudden cardio-pulmonary arrest (b) (6) days after his dose of peramivir and could not be resuscitated. No autopsy was performed, but a postmortem computed tomography scan did not reveal a clear cause of sudden death.
  - A 92-year-old woman with renal impairment and heart failure developed influenza and received 1 dose of peramivir. She died the (b) (6) day, and no autopsy was performed.

- *Torsade de Pointe*
  - An 87-year-old woman with hypertension and asthma (on theophylline) was found on the floor in her home. When she was brought to the emergency department, she had fever, dehydration, and unrest. Subsequently, she was diagnosed with influenza B, sedated with IV midazolam and dexmedetomidine, and intubated. She was noted to have a prolonged QT interval, but it was unclear if this was present prior to peramivir administration. She developed torsade de pointe, which was treated and resolved.

- *Convulsion*
  - A 72-year-old woman with advanced dementia was diagnosed with influenza and given peramivir. (b) (6) later, she developed a seizure and was taken to the hospital, where she was treated with diazepam. Her temperature at the time of the event was 39°C.

In addition, one case of Stevens-Johnson syndrome and two cases of exfoliative dermatitis were reported in postmarketing (see Section 7.3.5 "Rash").

Postmarketing Safety Surveillance Studies

Three post-approval observational studies were conducted in Japan: one in adults, one in pediatrics (see Section 7.6.3), and one in patients with high-risk factors (pregnancy, underlying disease, elderly ≥ 65 years of age); only the latter is still ongoing.

- The adult observational study was conducted between October 2010 and February 2012 and enrolled 1,309 patients at 193 institutions in Japan. The safety evaluable population was 1,174, with even distribution by gender. The majority of patients were between 15 and 65 years of age; 11% were ≥ 65 years old and 6% were < 15 years old. Almost all patients (98%) received peramivir within 2 days of the start of influenza symptoms; 98% of patients received only 1 day of peramivir treatment. Most patients were treated in an outpatient setting, but 3% were hospitalized for influenza, and 5 patients had serious influenza defined as either influenza encephalopathy or the need for mechanical ventilation.

  A total of 51 patients (4%) experienced 78 AEs deemed related to peramivir by the prescribing physicians; all were non-serious and there were no fatal AEs reported. Most of the AEs (91%) occurred within 3 days of peramivir treatment and nearly all (99%) were resolved or improved. The most common AEs were diarrhea (22 events), vomiting (10 events), and nausea (8 events). There were no significant differences in AE incidence by age group, and no new safety events were identified.

- The safety surveillance study in patients with high-risk factors was initiated in January 2010 and is still ongoing. The study has enrolled 759 of a planned 600 patients as of September 2013. Interim data are available on 193 patients from 109 institutions. The majority of patients (54%) were elderly and 23% were < 15 years of age; there was a single pregnant woman in this study. Most patients (88%) received peramivir within 2 days of the start of influenza symptoms and nearly all were hospitalized; only one patient was treated in an outpatient setting. Ten patients (5%) had serious influenza, defined as influenza encephalopathy or need for mechanical ventilation. Most patients (79%) received 1 day of peramivir, while 15% received 2 days, 5% received 3 days, and 2% received ≥ 4 days.

> A total of 34 patients (18%) experienced 54 AEs deemed related to peramivir by the prescribing physicians. There were four SAEs: viral myositis, AST increased, neutrophil count decreased, and white blood cell count decreased. There were no fatal AEs reported. The incidence of AEs in patients aged ≥ 65 years was 21% compared with 11% in patients < 15 years of age; the incidence of AEs in other age groups was not reported. No AEs were reported in the four patients < 2 years of age or in the pregnant woman. About half of the AEs occurred within 3 days of start of peramivir treatment. Most AEs (91%) resolved or improved, but two events were reported as unresolved. The most common AEs in this cohort were AST increased (13 events) and ALT increased (11 events). No new safety signals have been found to date.

In Korea, peramivir is currently being used only in a safety surveillance protocol. All AEs are mandated by the protocol to be reported on case report forms regardless of attribution, and there are no spontaneous reports. There have been 468 patients treated with peramivir from approval in August, 2010 through the 2012-2013 influenza season. There have been 4 SAEs and 11 non-serious AEs reported in this study, all of which were seen during clinical development.

In conclusion, the postmarketing data with peramivir indicate a low rate of adverse event reporting given the large number of patients treated since 2010, and a safety profile similar to that seen during clinical development. Potential new safety signals noted in Japan post-approval; e.g. hepatic toxicity, shock, anaphylaxis, and haemorrhagic colitis, have not borne out upon closer inspection of the clinical data, most of which were confounded. Neuropsychiatric events and severe rash events, however, have been reported in cases such that a role for peramivir cannot be excluded.

9 Appendices

Table 46: Subject Disposition - Study 0815T0631

	S-021812 300 mg N=366	S-021812 600 mg N=368	Oseltamivir N=365
Completed	341 (93.2%)	350 (95.1%)	347 (95.1%)
Discontinued	25 (6.8%)	18 (4.9%)	18 (4.9%)
- Ineligibility as a study subject	1 (0.3%)	3 (0.8%)	0 (0.0%)
- Lost to follow-up	2 (0.5%)	1 (0.3%)	0 (0.0%)
- Subject's request	10 (2.7%)	4 (1.1%)	8 (2.2%)
- Adverse event	9 (2.5%)	10 (2.7%)	9 (2.5%)
- Other	3 (0.8%)	0 (0.0%)	1 (0.3%)

Source: Clinical Study Report 0815T0631

Table 47: Subject Demographics (Treated Subjects) - Study 0815T0631

		S-021812 300 mg N=364	S-021812 600 mg N=364	Oseltamivir N=365
Region	Japan	247 (67.9%)	249 (68.4%)	246 (67.4%)
	Republic of Korea	36 (9.9%)	34 (9.3%)	35 (9.6%)
	Taiwan	81 (22.3%)	81 (22.3%)	84 (23.0%)
	Hong Kong	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnic Group	Hispanic or Latino	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Hispanic or Latino	364 (100.0%)	364 (100.0%)	365 (100.0%)
Race	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	364 (100.0%)	364 (100.0%)	365 (100.0%)
	Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
	White	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age (years)	N	364	364	365
	Mean	34.9	35.9	34.6
	SD	11.7	11.9	11.7
	Min	20.0	20.0	20.0
	Median	32.0	33.5	32.0
	Max	78.0	78.0	80.0
	20 - 29	151 (41.5%)	136 (37.4%)	150 (41.1%)
	30 - 39	99 (27.2%)	110 (30.2%)	110 (30.1%)
	40 - 49	69 (19.0%)	65 (17.9%)	62 (17.0%)
	50 - 59	30 (8.2%)	34 (9.3%)	30 (8.2%)
	60 - 64	7 (1.9%)	11 (3.0%)	4 (1.1%)
	65 -	8 (2.2%)	8 (2.2%)	9 (2.5%)

BMI (kg/m^2)	N	364	364	365
	Mean	22.59	22.78	22.54
	SD	3.82	3.81	3.80
	Min	15.05	16.02	16.23
	Median	21.79	21.98	21.77
	Max	39.13	40.95	47.36
	- <18.5	33 (9.1%)	29 (8.0%)	31 (8.5%)
	18.5 - <25.0	248 (68.1%)	249 (68.4%)	256 (70.1%)
	25.0 - <30.0	66 (18.1%)	63 (17.3%)	61 (16.7%)
	30.0 - <35.0	13 (3.6%)	19 (5.2%)	15 (4.1%)
	35.0 - <40.0	4 (1.1%)	3 (0.8%)	0 (0.0%)
	40.0 -	0 (0.0%)	1 (0.3%)	2 (0.5%)
Gender	Male	180 (49.5%)	199 (54.7%)	184 (50.4%)
	Female	184 (50.5%)	165 (45.3%)	181 (49.6%)
Smoking status	Currently	113 (31.0%)	112 (30.8%)	112 (30.7%)
	Formerly	35 (9.6%)	36 (9.9%)	32 (8.8%)
	Never	216 (59.3%)	216 (59.3%)	221 (60.5%)
Current smoking behavior	No	251 (69.0%)	252 (69.2%)	253 (69.3%)
	Yes	113 (31.0%)	112 (30.8%)	112 (30.7%)
History of alcohol consumption	Daily	38 (10.4%)	51 (14.0%)	43 (11.8%)
	Occasionally	161 (44.2%)	161 (44.2%)	167 (45.8%)
	Formerly	24 (6.6%)	16 (4.4%)	16 (4.4%)
	Never	141 (38.7%)	136 (37.4%)	139 (38.1%)
Inpatient / outpatient	Outpatient	361 (99.2%)	356 (97.8%)	359 (98.4%)
	Inpatient	3 (0.8%)	8 (2.2%)	6 (1.6%)
Complication	No	237 (65.1%)	218 (59.9%)	233 (63.8%)
	Yes	127 (34.9%)	146 (40.1%)	132 (36.2%)
Previous drug	No	158 (43.4%)	150 (41.2%)	154 (42.2%)
	Yes	206 (56.6%)	214 (58.8%)	211 (57.8%)
Previous therapy	No	351 (96.4%)	356 (97.8%)	351 (96.2%)
	Yes	13 (3.6%)	8 (2.2%)	14 (3.8%)
Duration of influenza (hours)	0 - 12	33 (9.1%)	24 (6.6%)	30 (8.2%)
	12< - 24	129 (35.4%)	118 (32.4%)	131 (35.9%)
	24< - 36	94 (25.8%)	115 (31.6%)	107 (29.3%)
	36< - 48	108 (29.7%)	106 (29.1%)	95 (26.0%)
	48< -	0 (0.0%)	1 (0.3%)	2 (0.5%)

Result of rapid antigen test	A	335 (92.0%)	335 (92.0%)	338 (92.6%)
	B	27 (7.4%)	29 (8.0%)	25 (6.8%)
	A and B	2 (0.5%)	0 (0.0%)	2 (0.5%)
Influenza vaccination	No	300 (82.4%)	308 (84.6%)	302 (82.7%)
	Yes	64 (17.6%)	56 (15.4%)	63 (17.3%)
Composite symptom scores at baseline	N	364	364	365
	Mean	12.5	12.5	12.5
	SD	3.4	3.3	3.2
	Min	4.0	5.0	6.0
	Median	12.0	12.0	12.0
	Max	21.0	21.0	21.0
	0 - 14	260 (71.4%)	263 (72.3%)	261 (71.5%)
	15 - 21	104 (28.6%)	101 (27.7%)	104 (28.5%)
Body temperature (deg C) at baseline	N	364	364	365
	Mean	38.53	38.48	38.56
	SD	0.49	0.49	0.52
	Min	38.00	38.00	36.00
	Median	38.40	38.30	38.40
	Max	40.30	40.00	41.00
Activity assessment (IIWS) at baseline	N	364	364	365
	Mean	4.0	3.7	3.8
	SD	2.1	2.0	2.0
	Min	0.0	0.0	0.0
	Median	4.0	3.0	3.0
	Max	10.0	10.0	10.0

Source: Clinical Study Report 0815T0631

9.1 Literature Review/References

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Louie J, Yang S, Yen C, Acosta M, Schechter R, Uyeki T. Use of intravenous peramivir for treatment of severe influenza A (H1N1)pdm09. PLoS ONE 2012; 7(6):e4026.

9.2 Labeling Recommendations

Key labeling recommendations as of this writing are outlined here; refer to the Cross-Discipline Team Leader (CTDL) Review by Dr. Linda Lewis for any subsequent labeling changes recommended after this review was completed.

- **1 INDICATIONS AND USAGE** - the following is recommended for the indication:
  - RAPIVAB (b) (4)

  To this, the following Limitations of Use are recommended:

  - Efficacy of RAPIVAB is based on clinical trials of naturally occurring influenza in which the predominant influenza infections were influenza A virus; a limited number of subjects infected with influenza B were enrolled.
  - Influenza viruses change over time. Emergence of resistance substitutions could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns

and treatment effects when deciding whether to use RAPIVAB *[see Microbiology (12.4)]*.

- RAPIVAB is not recommended in patients with serious influenza requiring hospitalization *[see Special Populations (8.7)]*

- **2 DOSAGE AND ADMINISTRATION** - although the pivotal Study 0722T0621 required IV peramivir to be administered over a 30 minute infusion period, other trials (e.g., Studies BCX1812-111 and 0815T0631) employed a 15 minute IV infusion time and observed no difference in safety. Therefore, the follow is recommended for dosage and administration:

  - The recommended dose of RAPIVAB in adult patients 18 years of age or older with acute uncomplicated influenza is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes.

  2.2 Dosing in Patients with Renal Impairment - (b) (4) the Clinical Pharmacology review team recommends a dose reduction for patients with baseline creatinine clearance below 50 mL/min due to significantly increased drug exposures observed when IV peramivir was administered to subjects with moderate to severe renal impairment.

- **5 WARNINGS AND PRECAUTIONS** - recommended language regarding serious skin reactions and neuropsychiatric events is below, revised from the Applicant's proposed language for clarity and consistency with other NAI drug labeling:

  5.1 Serious Skin/Hypersensitivity Reactions

  - Rare cases of serious skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with RAPIVAB in clinical studies (b) (4) in postmarketing experience. Appropriate treatment should be instituted if a serious skin reaction occurs or is suspected.

  5.2 Neuropsychiatric Events

  - Influenza can be associated with a variety of neurologic and behavioral symptoms that can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur in uncomplicated influenza as well.

    There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including RAPIVAB. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be

made, but they appear to be uncommon. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of RAPIVAB to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior.

- **6 ADVERSE REACTIONS** - it is recommended that this section only include the AEs observed with the 600 mg dose of peramivir (IV or IM) in the five controlled trials of acute uncomplicated influenza. In addition, it is recommended that the adverse reactions table only list clinical AEs and not laboratory-related AEs; a separate table for graded laboratory toxicities is recommended. Lastly, safety information from the hospitalized trials is to be removed from this section and included in a separate subsection under Section 8 Use in Specific Populations (see below).

- **8 USE IN SPECIFIC POPULATIONS**
  8.7 Patients with Serious Influenza Requiring Hospitalization - the following text is recommended regarding (b) (4)

  - (b) (4)

    Use of RAPIVAB was not shown to provide treatment benefit in this population.

- **14 CLINICAL STUDIES** - for the description of the pivotal Study 0722T0621, (b) (4)

9.3 Advisory Committee Meeting

Review of this application did not warrant convening an Advisory Committee Meeting as peramivir is not a first-in-class drug and there is ample clinical experience with other NAI drugs.

9.4 Clinical Investigator Financial Disclosure Review

Application Number: NDA 206426
Submission Date(s): December 23, 2013
Applicant: BioCryst Pharmaceuticals, Inc.
Product: RAPIVAB (peramivir injection)

Reviewer: Peter Miele, MD
Date of Review: August 23, 2014
Covered Clinical Study (Name and/or Number): Studies 0722T0621, BCX1812-211, BCX1812-212, or BCX1812-311

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 906		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 64		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The Applicant certified that it has not entered into any financial arrangement with investigators participating in Studies 0722T0621, BCX1812-211, BCX1812-212, or BCX1812-311 whereby the value of compensation to the investigator could be affected by study outcome. Certification was available for 93% (842/906) of the investigators participating in these four clinical trials. Of these, no investigator was identified with disclosable financial interests/arrangements with BioCryst or Shionogi, as described in

21 CFR 54.2 (a), (b), (c) and (f). For the 64 investigators or sub-investigators for which certification was not available, the Applicant certified that it acted in due diligence to obtain the required information and that it was not possible to do so. For the three BioCryst-sponsored trials, none of the investigators missing financial disclosure information were from sites that enrolled more than 2% of the subject population for the respective trial. In the Shionogi-sponsored trial (0722T0621), the majority of investigators missing financial disclosure forms were from sites that enrolled ≤ 4% of the total subject population for that trial. However, three sub-investigators missing financial disclosure information were affiliated with one particular site that enrolled 31 subjects, or 10% of the study population. This site had a total of 12 investigators or sub-investigators and none of the other nine investigators had disclosable financial interests with Shionogi or BioCryst; thus, it is unlikely that the three missing sub-investigators did. Moreover, the use of randomization in each of these trials, as well a composite primary endpoint based on patient-reported outcomes (time to alleviation of all seven symptoms), reasonably mitigates the potential for bias due to financial interests.

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

/s/

PETER S MIELE
08/22/2014

MARY E SINGER on behalf of LINDA L LEWIS
08/22/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206426 **Applicant: BioCryst** **Stamp Date: December 23, 2013**

Drug Name: Peramivir **NDA/BLA Type: Original**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			eCTD, AdAM
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	√			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	√			
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			See Section 6 of Clinical Overview (Module 2.5)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: 0722T0621 Study Title: Phase II Clinical Study of Single-Dose Intravenous S-021812 in Patients with Influenza Virus Infection - A Double-Blind, Parallel Group, Comparative Dose-Finding Study Sample Size: 300 Arms: 300 mg, 600 mg, PBO Location in submission: Module 5.3.5.1 Study Number: BCX1812-211 Study Title: A Phase II, multicenter, randomized,	√			There are two Phase 2 dose-ranging trials, one evaluating 300 and 600 mg IV peramivir and one evaluating 150 and 300 mg IM peramivir. In addition, a Phase 2 trial of 600 mg IM peramivir and a Phase 3 trial of 300 mg IM peramivir were conducted. Two bioavailability trials

	Content Parameter	Yes	No	NA	Comment
	double-mask, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza. Sample Size: 344 Arms: 150 mg, 300 mg, PBO Location in submission: Module 5.3.5.1 Study Number: BCX1812-212 Study Title: A Phase II, multicenter, randomized, placebo-controlled, study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated acute influenza. Sample Size: 405 Arms: 600 mg, PBO Location in submission: Module 5.3.5.1 Study Number: BCX1812-311 Study Title: A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza. Sample Size: 82 Arms: 300 mg, PBO Location in submission: Module 5.3.5.1				(BCX1812-111 and -113) demonstrate the bioequivalence of the IM and IV peramivir formulations. If the IM trials are used to support the efficacy and safety of IV peramivir, then the BA trials are pivotal as well.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Study 0722T0621: Phase II Clinical Study of Single-Dose Intravenous S-021812 in Patients with Influenza Virus Infection - A Double-Blind, Parallel Group, Comparative Dose-Finding Study Indication: treatment of acute uncomplicated influenza Pivotal Study #2 Indication:		√		Study 0722T0621 is identified as the sole pivotal study for this NDA as it is the only adequate and well - controlled trial to evaluate IV peramivir at the dose and schedule proposed for the indication. However, the three IM peramivir studies listed in #13 are also adequate and well-controlled studies and may provide supportive efficacy information. (Studies BCX1812-111 and -113 demonstrate the bioequivalence of the IM and IV peramivir formulations.) At a Type C meeting held on April 2, 2013, the Division agreed that Study 0722T0621, in combination with pooled supporting data from BCX1812-211 and BCX1812-311,

	Content Parameter	Yes	No	NA	Comment
					could be submitted to support an NDA.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	√			See Section 4.5 and 5.9 of the Clinical Overview (Module 2.5). The data to support peramivir use in acute uncomplicated influenza come in large part from studies conducted in Asian subjects. With the exception of weight, BMI, and prevalence of smoking, U.S. and Asian populations had similar demographic and other baseline characteristics. The standard of care and level of care in Japan, Taiwan, and Korea are comparable to the U.S. In addition, data collection methods in the Asian studies were comparable to studies run in the US and study parameters, including inclusion and exclusion criteria, were similar. The pivotal Study 0722T0621was conducted in Japan in accordance with Good Clinical Practice (GCP). As part of the Pre-Emergency Use Authorization (EUA) activities of 2009, FDA inspected three

	Content Parameter	Yes	No	NA	Comment
					clinical sites that participated in Study 0722T0621, Shionogi Headquarters (sponsor of the study), as well as the Contract Research Organization (CRO) that conducted the study. No major observations resulted from these inspections.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	√			Study BCX1812-106 was a thorough QT (TQT) study. Results were reviewed by QT-IRT (IND 69038, SDN 133, 12/07/2009). No significant QTc prolongation effect of peramivir (600 mg and 1200 mg) was detected in this TQT study.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			Postmarketing data from Japan and Korea are included, as well as experience from the Emergency IND program and EUA of 2009. In addition to the U.S., peramivir IV has also been used in other countries under emergency situations, including Israel, Australia, Mexico, and Hong Kong. Limited information from these countries is available. Peramivir is also approved for use in China (b) (4)
21.	For chronically administered drugs, have an adequate			√	

	Content Parameter	Yes	No	NA	Comment
	number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			The proposed efficacious dose of IV peramivir is 600 mg administered as a single dose. In 2009, the Division noted that a safety database of 1000 subjects with acute uncomplicated influenza treated with IV/IM 600 mg peramivir and 500 hospitalized subjects treated with IV 600 mg peramivir daily for ≥ 5 days would be reasonable to file an NDA. This was in the context of a dual indication for acute uncomplicated and hospitalized influenza infection that was proposed at the time. Currently, the only indication being sought is treatment of acute uncomplicated influenza. A total of 685 adult subjects with acute uncomplicated influenza have been treated with 600 mg IM/IV peramivir; if the 300 mg dose is considered, then 1340 such subjects have been exposed. The pooled safety population of subjects who have received at least 1 dose of ≥ 600 mg IV/IM, including hospitalized subjects,

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
					is 1128 subjects; 1890 subjects if ≥ 300 mg IV/IM is considered. In addition, data from the EUA and other postmarketing experiences are available to inform the safety assessment.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		√		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			Neuraminidase inhibitor (NAI) class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			See Section 5.6 of Integrated Summary of Safety (Module 5.3.5.3)
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			A Pediatric Study Plan is submitted (Module 1.9.6). A deferral to conduct pediatric studies is requested.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	√			See Section 1.3.1.4 of Risk Management Plan (Module 1.16)
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	√			See #17
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			See Section 5.6 of Integrated Summary of Safety (Module 5.3.5.3)
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			See Section 5.6 of Integrated Summary of Safety (Module 5.3.5.3)
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

1. We have noticed across multiple studies that numerous subjects have more than one laboratory test result reported for the same lab test name, date and time. This appears to affect predominantly the reporting of neutrophil counts and neutrophil/leukocyte ratios. Furthermore, the duplicated test results are widely divergent from one another for a given subject, lab test, date and time and also appear to use different reference ranges. These duplicated test results are not flagged in any easily identifiable manner, so that it would be difficult to extract them if necessary to conduct our analyses. The enclosed Excel spreadsheet includes the subjects, by subject ID and trial, and the laboratory tests we have identified with multiplicity of reported results.

   Please explain the occurrence of these duplicate test results and the disparity in the reported results and reference ranges used. If there is a manner in which we can easily identify these instances of duplicate test reporting, please describe. If not, please resubmit the laboratory tabulation datasets with a flag variable to identify those instances of duplicate reporting, particularly for Studies BCX1812-211, -212, and -311. Also, when multiple results are reported for a given subject, test, date and time, please identify which result is to be relied upon for our review. Lastly, please define the "LOINC Code" variable, as the define file does not.

2. Please include the following information in a tabular format for each of the supportive clinical trials (BCX1812-211, BCX1812-212, and BXC1812-311).

   By site, please list:
   a. Number of subjects screened
   b. Number of subjects randomized
   c. Number of subjects excluded from study, include reasons not randomized
   d. Number of subjects randomized but not treated, include reasons not treated
   e. Number of subjects treated who prematurely discontinued study, include reasons for discontinuation
   f. Number of protocol violations, include descriptions of violations
   g. Number of AEs
   h. Number of SAEs
   i. Number of deaths
   j. Number of subjects who met primary endpoint efficacy parameter, include percentage of randomized subjects

Peter Miele, MD	January 31, 2014
Reviewing Medical Officer	Date
Linda Lewis, MD	January 31, 2014
Clinical Team Leader	Date

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

/s/

PETER S MIELE
01/31/2014

LINDA L LEWIS
02/03/2014