CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206426Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 7, 2014
From	Linda L. Lewis, M.D. Division of Antiviral Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	206426/000 Original NDA
Applicant	BioCryst Pharmaceuticals, Inc.
Date of Submission	December 23, 2013
PDUFA Goal Date	December 23, 2014
Proprietary Name / **Established (USAN) names**	Rapivab®/peramivir
Dosage forms / Strength	200 mg (20 mL) vial for injection
Proposed Indication(s)	1. Treatment of acute, uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days
Recommended:	***Approval*** *– with modifications in labeling as described in this review; contingent upon successful completion of all pending manufacturing site inspections*

1. Introduction

Peramivir (Rapivab®) is the third in the class of influenza neuraminidase inhibitors (NI) to be submitted for review. Inhibiting neuraminidase blocks release of new influenza viral particles from infected cells and may limit spread of virus through respiratory tract mucus. While the mechanism of action of peramivir is similar to that of the approved NIs oseltamivir (Tamiflu) and zanamivir (Relenza), its long half-life allows administration as a single intravenous (IV) dose. The Applicant, BioCryst Pharmaceuticals, seeks an indication for the treatment of acute uncomplicated influenza in adult patients who have had symptoms for up to 48 hours.

The Applicant submitted the results of Study 0722T0621, a single adequate and well-controlled trial evaluating two doses of IV peramivir compared to an IV placebo. This study was conducted entirely in Japan by the Japanese pharmaceutical sponsor Shionogi & Co., Ltd. Additional clinical trials using an intramuscular (IM) formulation or peramivir were conducted by BioCryst and also submitted as supportive of the primary indication. The Applicant provided a complete portfolio of nonclinical virologic, toxicologic and toxicokinetic, and clinical pharmacology studies to support safe and effective use of peramivir in humans.

This CDTL Review will summarize the findings of the FDA multi-disciplinary team of reviewers, describe the conclusions and recommendations presented by all disciplines, discuss any unresolved review issues, and provide an overall risk-benefit assessment of the drug.

2. Background

The regulatory history of peramivir is complicated. It was discovered by BioCryst and initially developed by RW Johnson Pharmaceutical Research Institute under a licensing agreement. The original IND for peramivir oral tablets (IND (b) (4) was submitted by RW Johnson in April, 1999, but development was terminated in 2001 because of (b) (4) An IND for an IV formulation (IND 69038) was filed in November, 2005 and the IND was granted Fast Track status shortly after. A separate IND for the IM formulation was filed in November, 2006. All rights were returned to BioCryst and development of the IV and IM formulations continued in collaboration with Shionogi.

Throughout development, peramivir has been evaluated in two settings: as a single dose for the treatment of acute uncomplicated influenza and in a multi-dose regimen for patients hospitalized with more severe influenza illness. Development of the IM formulation was limited by dose-limiting injection site pain and reactions as the dose-finding studies suggested a dose of two 2 mL injections were needed. The IV formulation elicited fewer injection site adverse events and was better tolerated at the 600 mg dose selected for final study. During development, (b) (4)

During the declared 2009 influenza H1N1 pandemic (pH1N1-2009) public health emergency, treatment of severely ill patients who required an IV formulation was considered an unmet medical need. Based on the results of the Shionogi Study 0722T0621, an Emergency Use Authorization (EUA) for use of peramivir in hospitalized patients with pH1N1-2009 was issued on October 23, 2009. Peramivir was distributed through the CDC to over 1200 hospitalized patients (adults, including some pregnant women, and children) at the request of their treating physicians. Many of these patients were critically ill and unable to tolerate approved oral or inhaled medications or had failed to respond to approved NAIs. The EUA distribution of peramivir continued until the end of the declared emergency in June, 2010. Following termination of the declared emergency, the FDA reviewed spontaneously reported adverse events but the available data did not allow an assessment of efficacy.

Peramivir was approved in Japan as Rapiacta® in January, 2010, for the treatment of viral infection with influenza type A and type B. The marketing authorization was extended to pediatric patients in October, 2010. It has also been approved in South Korea (as PeramiFlu®, August, 2010) for the treatment of adults with influenza A and B viruses, including pH1N1-2009 and avian influenza, although it is not currently marketed. No restrictions have been placed on marketing due to safety concerns in the countries where it is currently approved.

As with the EUA, the current NDA is also based primarily on the positive results of Study 0722T0621 (conducted by Shionogi) with additional supportive data from Studies BCX1812-211, BCX1812-212, BCX1812-311 (all conducted by BioCryst), and several other clinical trials. None of supportive studies individually met their pre-specified efficacy endpoints. The Applicant also submitted the results of Studies BCX1812-301 and BCX1812-303, two randomized controlled trials of peramivir in subjects with influenza severe enough to require hospitalization as informative to the NDA. The Review Team agreed to accept filing of the NDA primarily on the basis of Study 0722T0621 because the trial was a rigorously designed, multi-center trial, included two dose levels of peramivir as well as a placebo control arm, the efficacy results were robust and consistent across subgroups, and there were identifiable explanations for the failures of some other trials to meet their endpoints.

3. CMC/Device

For a complete description of the CMC information submitted and reviewed, please refer to the CMC Review submitted by Dr. Fuqiang Liu. This CDTL will summarize the major points from his review.

- *General product quality considerations*

As noted in the CMC Review, peramivir drug substance has five chiral centers and is a (b) (4). Drug substance specifications were submitted and found to be adequate, including tests for appearance, identification, assay, impurity content, organic volatile impurities/residual solvents, heavy metals, (b) (4) water content, pH, microbial limits, and bacterial endotoxin. The stability data submitted were found to be acceptable;

levels of total and individual impurities remained stable and no degradation products were observed.

The drug product, peramivir for IV injection, is a clear, colorless, isotonic, sterile solution containing 10 mg/mL of peramivir in 0.9% sodium chloride. Drug product is packaged as 200 mg in a 20 mL glass vial with appropriate stopper and seal. Specifications for drug product are acceptable and include description, identification, assay, degradation products, pH, osmolarity, particulate matter, sterility, and bacterial endotoxin. Drug product is very stable over time with no degradant observed at greater than (b) (4)%. Stability data submitted with the NDA support a shelf-life of 60 months for drug product. As the dose proposed for treatment is 600 mg, drug product is supplied in a carton containing three vials.

- *Facilities review/inspection*

Drug substance is manufactured and tested by (b) (4). Additionally, testing is also performed at (b) (4) Necessary inspections of all drug substance facilities have been completed and are acceptable.

Drug product is manufactured and tested at only a single site, (b) (4) This site has had a troubled inspection history over the past two years following documentation of multiple significant deficiencies identified on FDA Form 483s. Subsequently, the facility's inspection status has been classified as OAI. (b) (4) is currently not manufacturing any drug products while they attempt to correct the 483 deficiencies. While a follow-up inspection is planned, this inspection will focus on whether the facility can demonstrate overall adherence to Good Manufacturing Practice standards and not on specific pre-approval product inspections. The Review Team does not believe (b) (4) will be able to respond adequately to the 483 deficiencies, take all necessary corrective actions, and schedule/pass a peramivir-specific inspection by the expected action date for this NDA. Therefore, the Office of Compliance has recommended a Withhold Approval status for peramivir until all issues at (b) (4) have been addressed adequately and a product-specific, pre-approval inspection has been conducted.

- *Other notable issues (resolved or outstanding)*

The conclusions of the CMC reviewer were that adequate information had been provided in the NDA to assess the manufacturing, controls and specifications, analytical methods, and stability for both drug substance and drug product. However, Dr. Liu could not recommend approval at this time due to the unresolved inspection deficiencies at the only drug product manufacturing site, (b) (4). As discussed with the Applicant at the Mid-Cycle Meeting teleconference, an alternative path available to the Applicant is to select a different contractor for manufacture of peramivir drug product but they have not chosen to take this approach.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted a complete battery of nonclinical studies (in vitro and in vivo) to characterize the safety profile of peramivir. For a complete description of the nonclinical information submitted and reviewed, please refer to the Pharmacology/Toxicology Review submitted by Dr. Kuei-Meng Wu. This CDTL will summarize the major points from his review.

- *General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).*

Peramivir was evaluated in animal toxicology studies as the IV formulation due to poor bioavailability of the drug. The drug has low level binding to plasma proteins in all species evaluated. It is not significantly metabolized and is not a substrate or inhibitor of cytochrome P450 enzymes or p-glycoprotein. Excretion is primarily through the kidney as unchanged drug.

Target organ toxicity was characterized in dose ranging, single- and multiple-dose studies conducted in multiple species. Rabbits appeared to be the most sensitive species for kidney toxicity, exhibiting findings of tubular dilatation, necrosis, and protein casts in cortical areas and dilated tubules with mineralization in corticomedullary junction areas. Multifocal tubular regeneration was observed. Abnormal liver function was also observed in rabbits with concurrent renal toxicity. Renal and liver toxicity were not observed in either monkeys or rats.

The Applicant also conducted a 4-week IV peramivir study in juvenile rats. In this study, peramivir demonstrated no specific toxic effects other than body weight reductions and did not affect development or behavior. In other studies of oral peramivir in juvenile rats and rabbits, dose-related changes in hematologic parameters (RBCs and neutrophils) and renal cortical tubular changes were noted at middle and high doses.

- *Carcinogenicity*

Because the development program for peramivir focused on single dose or short courses of drug, concern for carcinogenicity was not high. Peramivir was negative in a series of genotoxicity studies including the Ames test, a mammalian chromosomal aberration assay, and a clastogenicity assay. A study evaluating carcinogenicity in rats was completed early in drug development and revealed no drug-related neoplasm.

- *Reproductive toxicology*

Reproductive toxicology was evaluated in both rats and rabbits. Among rats receiving the "maximal feasible dose" by IV infusion, there were no clear developmental malformations in the offspring. A finding of reduced renal papillae and dilated ureters was observed but is not considered a definitive malformation; it may represent a delay in development of the

urinary tract. Among rabbits, no fetal malformations were observed but there was maternal renal toxicity that was dose-limiting.

- *Other notable issues (resolved or outstanding)*

Overall, the nonclinical safety profile of peramivir was acceptable and none of the animal toxicity observed was considered worrisome in the context of a single-dose regimen for treatment of influenza. The Pharmacology/Toxicology reviewer recommended approval of peramivir for the proposed indication and did not identify a need for any additional nonclinical studies.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted a series of studies to characterize the pharmacologic profile of peramivir to allow safe and effective use. For a complete description of the clinical pharmacology information reviewed and the FDA's pharmacometrics analyses, please refer to the Clinical Pharmacology Review submitted by Drs. Leslie Chinn, Jeffry Florian, and Islam Younis. This CDTL will summarize the major points from their review.

- *General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.*

Oral peramivir is poorly absorbed and for this reason, the IV formulation was identified as the primary formulation for clinical development. Following administration of a single IV dose, the half-life of peramivir in healthy volunteers was about 20 hours. No accumulation of drug was observed in multiple-dose studies following either once or twice daily dosing. Peramivir exposure increased linearly with doses from 50 mg to 1200 mg. Binding to plasma proteins was shown to be low (< 5% in clinical plasma samples) and the drug did not partition into red blood cells. The PK profile in patients with influenza illness was similar to that observed in healthy volunteers and inter-individual variability was low (15-20%). Based on the clinical pharmacology program, the Applicant proposes a dosing regimen of a single dose of peramivir 600 mg given by intravenous infusion over at least 15 minutes.

The Applicant also developed an IM formulation but discontinued this development program (b) (4) Study BCX1812-113 was submitted to support their assertion that the peramivir exposure provided by IM administration was similar to that of IV administration. The Clinical Pharmacology reviewer agreed with the Applicant's conclusion that a dose of peramivir 600 mg IM was bioequivalent to a dose of 600 mg IV. The point estimate of mean AUC_{inf} was almost identical and the 90% CI of the ratio of geometric mean of IM to IV was 97.7-103.5%, well within the required 80% to 125% criteria. Peramivir C_{max} was approximately 28% higher following IV infusion compared to IM administration, an expected finding when comparing an IV route of administration to IM. Concentrations of peramivir measured in either nasal wash or throat gargle samples were variable but comparable following either IV or IM administration. The bioanalytic

site involved in the conduct of Study BCX1812-113 was inspected and no significant deficiencies were identified. This confirmed bioequivalence of peramivir regardless of whether administered by the IV or IM route allowed the Review Team to pool safety data from clinical trials using either route of administration.

- *Drug-drug interactions*

Because it is not a substrate or inhibitor of hepatic enzymes or known drug transporters, peramivir was not expected to have significant drug-drug interactions. The Applicant evaluated the potential for drug-drug interactions between peramivir and rimantidine, oseltamivir, a representative oral contraceptive (levonorgestrel/ethinyl estradiol), and probenecid.

- *Pathway of elimination*

Peramivir is eliminated almost entirely through the kidneys. In clinical trials, the fraction of peramivir excreted renally ranged from 76% to 97% within 7 days after single-dose administration in subjects with normal renal function. It is excreted as unchanged drug and no metabolites have been identified in plasma or urine. Excretion is correlated with creatinine clearance indicating elimination by glomerular filtration rather than tubular secretion.

- *Briefly comment on each of the critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment.*

Neither age nor gender was expected to have significant effects on peramivir exposure. Study BCX1812-104 conducted in otherwise healthy elderly subjects confirmed that exposure was increased by about 30% in elderly subjects compared to non-elderly, a level not requiring dose adjustment. Population PK analyses suggested that gender (in addition to weight) might have had a minor effect on exposure. Because it is not metabolized by hepatic enzymes, hepatic impairment was not expected to alter exposure and was not specifically evaluated. In population PK assessments, both weight and Asian race were identified as having a small effect on PK variability but these were not considered clinically meaningful.

As noted, peramivir is almost entirely excreted via the kidneys and renal impairment was expected to have a significant impact on exposure. Drug exposure was evaluated in subjects with mild, moderate, and severe renal impairment, including end-stage renal disease, in Study BCX1812-105. In this study, a single dose of 2 mg/kg IV was administered. The Applicant reported mean peramivir AUCs for subjects with mild, moderate, and severe renal impairment were 1.4-, 4.1-, and 5.5-fold higher, respectively, than the AUC in subjects with normal renal function. The FDA Pharmacometrics reviewer confirmed estimates of substantially higher drug exposure in the setting of renal impairment. (b) (4) they recommended a dose reduction of peramivir to 200 mg for patients with estimated creatinine clearance between

30 to < 50 mL/min and to 100 mg for patients with estimated creatinine clearance < 30 mL/min. These adjusted doses are expected to provide exposures matching that of subjects with normal renal function receiving 600 mg, the dose for which safety and efficacy were established (see Table 1). (b) (4)

Table 1: Predicted systemic peramivir exposure in patients with renal impairment based on simulation (population PK model)

Population	Dose (mg)	Median AUC (ng*h/mL)	AUC IQR[a] (ng*h/mL)
Normal renal function ($CL_{CR} \geq 80$ mL/min)	600	92,650	75,373-113,596
Mild renal impairment (CL_{CR} 50 to <80 mL/min)	600	124,937	156,014-194,143
Moderate renal impairment (CLCR 30 to <50 mL/min)	200	86,401	69,045-106,857
Severe renal impairment (CLCR 10 to <30 mL/min)	100	99,133	71,045-146,532

[a] IQR, interquartile range
Source: Abstracted from Clinical Pharmacology Review NDA (b) (4) Leslie Chinn (lead author), page 24.

In patients who require hemodialysis, 80% of the dose of peramivir is removed by the dialysis exchange. For this reason, peramivir should be dosed prior to hemodialysis if possible. In the event the dose must be given prior to hemodialysis, plasma concentrations are likely to still be adequate to inhibit viral replication and the half-life will be prolonged, so a second post-hemodialysis dose is not considered necessary.

- *Discuss relevant issues related to clinical pharmacology arising from investigations by gender, age, including pediatrics and geriatrics, and other demographic-based investigations.*

The Applicant conducted clinical pharmacology studies to characterize the PK profile of peramivir in multiple populations including healthy volunteers and subjects infected with influenza, subjects with renal impairment, and healthy elderly subjects. Neither age, race, nor gender appear to have a clinically significant effect on peramivir exposure as noted above.

The Applicant submitted results from a clinical trial evaluating a dose of peramivir 10 mg/kg IV in Japanese pediatric patients. Because a pediatric indication was not being requested, the Clinical Pharmacology Team did not review these data in detail.

- *Thorough QT study or other QT assessment*

The Applicant conducted a thorough QT study (BCX1812-106) evaluating single doses of peramivir 600 mg and 1200 mg in comparison to placebo and moxifloxacin (positive control) in healthy volunteers. The study results were submitted to the IND and were reviewed by the CDER Interdisciplinary Review Team for QT Studies in June, 2010. The IRT reviewer found the study design to be acceptable and concluded peramivir at twice the therapeutic dose had no clinically relevant effect on the QTc interval.

- *Other notable issues (resolved or outstanding)*

As part of the Clinical Pharmacology Review, the Pharmacometrics Review describes evaluations done of dose-response for efficacy and confirms the Applicant's selection of 600 mg as the optimal dose regimen. Because there were few adverse events reported more frequently in subjects receiving peramivir compared to placebo, a formal dose-response analysis for safety was not conducted.

The Pharmacometrics reviewer performed independent analyses to assess the choice of peramivir 600 mg rather than 300 mg as the appropriate dose for treatment. The reviewer conducted PK/PD simulations to assess the length of time the peramivir plasma concentrations remained above a random sampling of IC_{50} values from influenza virus isolates collected during the clinical trials. This analysis was undertaken because both doses demonstrated clinical efficacy based on an endpoint of time to alleviation of symptoms. In the PK/PD analysis, the 600 mg dose provided peramivir concentrations that remained above the IC_{50} for 39 hours compared to 29 hours with the 300 mg dose. The longer time above IC_{50} was considered to provide a plausible benefit of antiviral activity in a larger percentage of patients.

The Clinical Pharmacology Review Team recommended approval of peramivir at the proposed dose. The Review Team proposed modifications in the recommended dosing for patients with calculated creatinine clearance < 50 mL/min (see Section 12 Labeling). There are no other unresolved Clinical Pharmacology issues and no additional drug-drug interaction studies will be requested.

6. Clinical Microbiology

The Applicant submitted an extensive portfolio of virology data from both cell culture and animal models of infection to characterize the mechanism of action, antiviral activity, and resistance profile of peramivir. For a complete discussion of the virology data submitted and reviewed, please refer to the Virology Review submitted by Drs. Takashi Komatsu and Eric Donaldson. This CDTL will summarize the major points from their review.

- *General considerations*

Influenza neuraminidase is essential in the release of progeny virus from infected cells and consequently, NIs block spread of influenza from infected cells to non-infected cells. Peramivir is the third drug in the class of neuraminidase inhibitors (NAIs) and was

designed to bind to conserved influenza neuraminidase residues. It has been shown to have activity in biochemical assays (the neuraminidase inhibition assay) and in cell culture against both influenza A and B at low nanomolar concentrations. However, in both types of assay systems, activity against influenza B is less than influenza A.

Influenza viruses resistant to peramivir could be selected in cell culture. In this case, reduced susceptibility to peramivir was a result of amino acid substitutions in either the viral neuraminidase or hemagglutinin. In some cases, amino acid substitutions emerged in the hemagglutinin (HA G141E, D195N and T197N) before the emergence of the neuraminidase resistance substitution (NA H275Y). In some instances, substitutions could be selected in hemagglutinin without accompanying neuraminidase substitutions (HA N63K and N145D).

Some peramivir resistance pathways confer cross-resistance to oseltamivir and/or zanamivir. Cross-resistance to oseltamivir is possible through more common pathways. Some of the hemagglutinin resistance substitutions selected in cell culture confer cross-resistance to other NAIs that will not be detected with the neuraminidase assay usually used to screen for resistance.

The resistance analyses included in the clinical trials were somewhat limited in scope. In Study 0722T0621, Shionogi sequenced the neuraminidase gene of selected isolates identified as having a pre-defined high IC_{50} based on a phenotypic analysis. These analyses may have missed identifying minor populations of resistant virus and clearly did not identify isolates with possible resistance substitutions in hemagglutinin. Based on the limited data available, FDA analyses confirmed the Applicant's findings. Only the NA H275Y substitution was identified in more than one subject infected with influenza A H1N1. Among subjects infected with influenza A H3N2, one subject developed the NA R292K substitution and one subject developed the NA N294S substitution, both previously associated with reduced susceptibility or resistance to NAIs.

The Applicant evaluated dose-response for virologic endpoints which were confirmed by FDA reviewers. In Study 0722T0621, the proportion of subjects infected with influenza A H1N1 who were not shedding virus at Day 3 was higher in both the 300 mg (56.8%) and 600 mg (71.0%) groups than in the placebo group (47.2%). The difference between the 600 mg group and placebo was statistically significant. Among subjects infected with influenza A H3N2, the proportion who were not shedding virus at Day 3 was higher in both the 300 mg (85.7%) and 600 mg (84.0%) groups than in the placebo group (54.2%). The difference between the 300 mg group, 600 mg group, and placebo were statistically significant. The Applicant conducted a pooled analysis of viral shedding in Studies BCX1812-211 and BCX1812-311 for the studied doses of 150 mg and 300 mg. Although these studies failed to reach their clinical efficacy endpoint, there was a significant dose-response demonstrated in mean reduction in viral titer over time between arms for influenza A H3N2. In addition, the proportion of subjects who were not shedding virus at Day 3 was higher in both the 150 mg (46%) and 300 mg (64.4%) groups than in the placebo group (39.1%). Multiple other analyses showed numerical trends in virologic endpoints that did not reach statistical significance but consistently suggested a dose-

response. These analyses helped the Review Team come to the conclusion that peramivir 600 mg should be the recommended dose.

- *Notable issues (resolved or outstanding)*

The Virology reviewers recommend approval of peramivir for the treatment of influenza A. Some issues remain unresolved at the time of completing the Virology Review and will be addressed in post-marketing studies. As noted in the Clinical Virology Review, the peramivir clinical trials failed to enroll a sufficient number of subjects infected with influenza B to allow analysis of efficacy with this subtype. While the mechanism of action of NIs suggests peramivir should have activity against influenza B strains, cell culture data demonstrates higher IC_{50} for these strains. Additional clinical data are needed to support use in influenza B. The Applicant will be asked to provide final resistance data collected in some of the supportive trials that were not submitted with the NDA. In addition, the Applicant will be asked to further evaluate the impact of substitutions in hemagglutinin on cross-resistance with oseltamivir and zanamivir and the potential impact of these changes on antigenicity and response to influenza vaccine.

7. Clinical/Statistical- Efficacy

To support the proposed indication, the Applicant submitted one adequate and well-controlled, pivotal, clinical trial (Study 0722T0621) and multiple supportive trials. The efficacy and safety analyses focused on four placebo-controlled trials conducted in adults with acute, uncomplicated influenza (Studies 0722T0621, BCX1812-211, BCX1812-212, and BCX1812-311). However, the NDA submission also included data from an active-control trial (Study 081T0631) comparing peramivir to oseltamivir and from studies in high-risk or hospitalized subjects (Studies 0816T0632, BCX1812-201, BCX1812-301, and BCX1812-303). These studies were reviewed in less detail and included in some of the safety analyses but were not relied upon for efficacy. In addition, the Applicant submitted an open-label safety trial in pediatric subjects which will be discussed in more detail in Section 10 of this review. As noted in Section 2 of this CDTL review, the regulatory history of this development program is complex and this package of clinical trials was agreed upon by the Applicant and DAVP after discussions beginning shortly after the 2009 influenza pandemic. For more detailed descriptions of the clinical trials designs, please refer to the Clinical Review (Section 5.2) submitted by Dr. Peter Miele.

Overall, both the Clinical and Statistical reviewers' independent analyses confirmed the Applicant's conclusions of effectiveness based on the pivotal clinical trial. They also both conducted integrated analyses of the four placebo-controlled trials. Dr. Thomas Hammerstrom, the Statistical Reviewer, conducted numerous analyses to assess the robustness of the results across dose levels and in different demographic subgroups. The following points summarize the key efficacy findings of the FDA's clinical and statistical reviewers.

The four randomized, placebo-controlled trials in adults with acute, uncomplicated influenza were similarly designed and evaluated the same clinical endpoint but extended over multiple

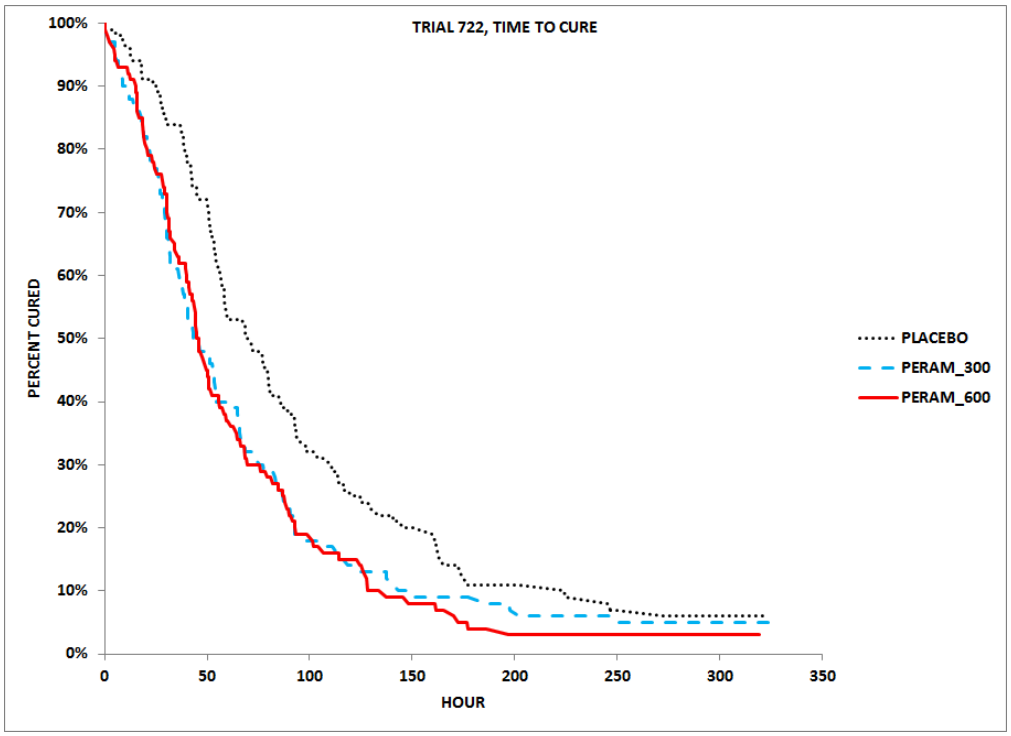
influenza seasons. These four trials evaluated peramivir doses of 150 mg, 300 mg, and 600 mg given either IV or IM. Because the IV and IM formulations provided similar peramivir exposures, results of the supportive IM trials could be pooled in some analyses. Of note, efficacy results of Study BCX1812-212 were not similar to the other three placebo-controlled trials, presumably because it was conducted during the 2008-2009 influenza season when the predominant circulating H1N1 strain was resistant to NAIs (NA H275Y substitution).

In the pivotal trial, adult subjects were eligible to enroll if they had fever > 38.0[c] (axillary) and at least two symptoms consistent with influenza illness with onset less than 48 hours before enrollment and a positive rapid antigen test (RAT) for influenza. Influenza infection was subsequently confirmed by viral culture, RT-PCR, or serology. In the supportive trials, enrollment criteria were similar with minor variations. The primary efficacy endpoint evaluated time to alleviation of symptoms (TTAS) based on self-reported symptoms of nasal congestion, sore throat, cough, aches and pains, fatigue (tiredness), headache, and feeling feverish graded on a 4-point severity scale (0/absent, 1/mild, 2/moderate, 3/severe) in subjects with confirmed influenza. Subjects recorded these symptoms on diary cards twice daily for the first 9 days, then once daily through day 14 and were instructed to record the severity of each symptom at that time. The TTAS endpoint analysis required that all symptoms be absent or mild and that alleviation of symptoms be sustained for a minimum of 21.5 hours.

Study 0722T0621 enrolled and treated 298 Japanese adults during the 2007-2008 influenza season. Subjects were randomized 1:1:1 to receive either placebo or peramivir at a dose of 300 mg or 600 mg. Baseline demographic and illness characteristics were balanced across the treatment arms. Influenza infection was confirmed by PCR in 99.7% of subjects with 72% having influenza A H1N1, 23% having influenza A H3N2, and 4% having either influenza B or an indeterminate influenza A. The mean age was 34.8 years, 51% were male, and 34% were smokers. The initial median composite symptom score was 11 with about 23% having scores greater than 14. Only 7 (2%) subjects discontinued the trial prematurely (1 in placebo arm, 2 in 300 mg arm and 4 in 600 mg arm).

In Study 0722T0621, a shorter TTAS was observed in both peramivir treatment arms compared to the placebo arm. Figure 1 below taken from Dr. Hammerstrom's Statistical Review shows the Kaplan-Meier curves generated for the TTAS analysis. As noted in Dr. Miele's Clinical Review, the median TTAS was 59.1 hours in the peramivir 300 mg group, 59.9 hours in the peramivir 600 mg group, and 81.1 hours in the placebo group. The treatment differences between both peramivir arms and the placebo arm were similar (-22.7 hours and -21.9 hours) and statistically significant.

Figure 1: Kaplan-Meier Curves for Time to Alleviation of Symptoms in Subjects with Confirmed Influenza – Study 0722T0621



Source: Statistical Review NDA 206426, T. Hammerstrom, Figure 3.2.1 A.

None of the supportive placebo-controlled trials met their primary clinical endpoints for efficacy. Study BCX1812-211 evaluated peramivir doses of 150 mg and 300 mg IM and while the TTAS for both doses was numerically shorter, neither dose was significantly better than for placebo. Study BCX1812-311 evaluated a dose of 300 mg IM and was otherwise similar to Study BXC1812-211. It was terminated early when the Applicant decided to focus on the 600 mg dose (b) (4)
As previously noted, Study BCX1812-212 was conducted during an influenza season when almost all influenza A H1N1 isolates were resistant to peramivir and other NAIs.

A pooled analysis of TTAS including all four placebo-controlled trials of acute, uncomplicated influenza was undertaken as a sensitivity analysis. Together, these trials contributed over 600 influenza-infected subjects receiving one of the three studied doses of peramivir and 400 infected subjects receiving placebo. In the integrated analysis, subjects with missing diary card information were excluded. Results from the pooled analysis are shown in Table 2 taken from Dr. Miele's Clinical Review. As shown, the pooled data from these trials, confirms that peramivir 600 mg leads to a median TTAS that is significantly shorter than placebo.

Table 2: Median Time to Alleviation of Symptoms by Treatment Group in Subjects with Confirmed Influenza - Pooled Placebo-Controlled Trials in Acute Uncomplicated Influenza

Kaplan-Meier Estimate	Peramivir 150 mg	Peramivir 300 mg	Peramivir 600 mg	Peramivir Overall	Placebo
N (number censored)	100 (17)	255 (33)	256 (22)	611 (72)	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: Abstracted from Clinical Review NDA 206426, P. Miele, page 65.

Using a different statistical method for integrated analysis, Dr. Hammerstrom evaluated the p-values obtained for the individual trials and synthesized a single p-value for pooled trials. Using this method, he assessed the pooled p-value for all infected subjects in the four placebo-controlled trials and for subjects with influenza virus expected to be susceptible (H1N1 wild type and H3N2). The pooled supportive trials have p-values of 0.26-0.29 after pooling when all infected subjects are included. If only influenza types expected to be susceptible are included in the analysis, the pooled p-values are 0.11-0.13, "nearly marginally significant." If the pivotal trial is included in the pooling, the pooled p-value is $< 4x10^{-4}$. His interpretation of this exercise was that "the BioCryst (supportive) studies are not collectively significant but they are supportive of efficacy in type A influenza without the H1N1 H275Y substitution. Combined with Trial 722, they are sufficient to demonstrate efficacy against Tamiflu susceptible strains of type A influenza."

In reviewing the Applicant's proposed dose selection, several of the key secondary efficacy analyses were informative. As noted in Section 6 of this CDTL, several virologic dose-response analyses suggested the peramivir 600 mg dose provides better antiviral activity.

Another of the secondary endpoints that appeared to support a dose-response was that of time to resumption of usual activities. This endpoint was assessed by self-report on a visual analog scale rating the patient's ability to perform usual activities; a score of 10 was considered fully returned to baseline "normal." In this analysis, the median time to resumption of usual activities was 11 days for the 150 mg dose arm, 8 days for the 300 mg dose arm, 6 days for the 600 mg dose arm, and 9 days for the placebo arm.

The Applicant also notes that both peramivir treatment arms demonstrated significant reductions in the median time to resolution of fever, one of their key secondary analyses. This analysis is complicated by use of slightly different methods for calculating the time to resolution of fever in different trials, so the Applicant recalculated all fever endpoints similarly. Using this unified methodology, no difference in fever resolution between peramivir and placebo was noted in Study BCX1812-212, the trial conducted during the season notable for circulating influenza resistant to NAIs. In pooled Studies BCX1812-211 and -311, both 300 mg and 600 mg doses shortened duration of fever by about 1 day compared to placebo. In

Study 0722T0621, the duration of fever was shorter in all arms compared to the other three trials but not different across arms. However, if the original Shionogi method of calculating resolution of fever in Study 0722T0621was used, both peramivir treatment arms had a shorter median time to resolution of fever than the placebo arm. (b) (4)

A corollary to the analysis of resolution of fever was an analysis of acetaminophen use. Acetaminophen use was a pre-specified secondary endpoint only for Study 0722T0621; the other three placebo-controlled trials of acute influenza did not capture acetaminophen dose information. In this pivotal study, mean number of doses of acetaminophen was 2.7, 2.6, and 3.5 in the 300 mg, 600 mg, and placebo arms, respectively, and total acetaminophen consumption was 849 mg, 776 mg and 1036 mg, respectively.

- *Subgroup analyses*

Both the Applicant and the FDA conducted subgroup analyses to assess efficacy according to demographic characteristics and baseline disease characteristics.

The Applicant evaluated the contribution of age as a factor possibly affecting efficacy by dividing the pooled population in the four placebo-controlled trials of acute uncomplicated influenza into three age groups: 12 to < 18 years, 18 to < 65 years, and 65 years or older. Their analysis was hampered by this choice of age subgroups in that about 98% of the study population was in the 18 to < 65 year age group. Less than 2% of the pooled study population was 65 years or older, making it impossible to make meaningful comparisons. The Applicant found no meaningful differences between male and female subjects but did note a smaller median difference in TTAS between peramivir and placebo among male subjects. They also noted larger reductions in TTAS among Asian subjects, with smaller numerical reductions among Caucasian subjects. The Applicant considered the subgroup of Blacks/African Americans too small to draw conclusions (about 15% of the pooled population). Similarly, as only about 25% of the pooled study population were smokers, the Applicant considered the number of subjects in this subgroup too small to assess this co-factor.

The FDA Statistical Reviewer explored demographic co-factors (divided by quartiles of subjects enrolled where appropriate) by pooling the four clinical trials and using different stratifying variables. For these analyses, all peramivir dose groups were pooled to provide larger subgroups. Age, sex, race, country/region of origin, and smoking status were explored. In addition, influenza subtype, duration of illness prior to treatment, and baseline symptom score were also evaluated. Dr. Hammerstrom's analysis suggested a decrease in effectiveness of peramivir compared to placebo with increasing age (by quartile), in Black subjects, and with later initiation of treatment after onset of symptoms. His analysis also suggested better effectiveness in Asia compared to other regions. For a full description of his subgroup analyses, please see Section 4 (Results in Special Populations) of the Statistical Review.

Review of the trials, provides possible explanations for some of the subgroup analysis findings. A majority of the Asian subjects were enrolled in Study 0722T0621 and in this trial, they presented earlier after onset of symptoms and with lower symptom scores than observed in other trials. As noted by the Applicant, the numbers of Black/African American subjects were relatively small and this subgroup may have been confounded by other interactions (age, type of influenza, later initiation of treatment, etc.) which were not evaluated. As noted above, subjects with later onset of symptoms (> 36 hours) had no improvement in TTAS with peramivir. Finally, both the Applicant and the FDA reviewers identified that peramivir does not appear to provide treatment benefit in subjects infected with influenza A H1N1 carrying the H275Y substitution.

- *Notable efficacy issues (resolved or outstanding)*

In general, one of the commonly stated reasons to recommend treatment of influenza is to prevent or ameliorate the occurrence of complications. Incidence of influenza complications was a secondary or exploratory endpoint in some of the trials of acute, uncomplicated influenza but none of these trials were large enough to provide an accurate assessment of this endpoint. None of the trials prospectively defined diagnostic criteria or management for conditions or events considered complications of influenza such as bronchitis, otitis media, pneumonia, and sinusitis. The rates of investigator-diagnosed complications varied widely across studies, from 2-3% in Study 0722T0621 to 19-20% in BCX1812-211, -311, and -212. For all these reasons, a reliable assessment of peramivir's impact on influenza complications is not possible based on the data submitted; however, no notable differences in rates of influenza complications were noted between subjects receiving peramivir and those receiving placebo.

In addition to treatment of acute, uncomplicated influenza, the peramivir development program was intended to provide evidence that the drug could be used to treat hospitalized patients with more severe influenza illness. Based on a small pilot trial (Study BCX1812-201), the Applicant conducted additional multi-national trials to evaluate hospitalized influenza patients. The Applicant submitted results from one randomized, placebo-controlled clinical trial of peramivir in patients with influenza requiring hospitalization and requested it be included in labeling.

Study BCX1812-301 randomized subjects 2:1 to receive blinded peramivir 600 mg or placebo daily for 5-10 days added on to the local standard care for influenza; in a subset of subjects standard of care was only supportive measures. A total of 405 adult and pediatric (> 6 years of age) subjects hospitalized for influenza were enrolled globally. The primary efficacy endpoint was time to clinical stability, defined as normalization of at least 4 of the following signs: temperature $\leq 37.2^{o}$C oral, oxygen saturation $\geq 92\%$, respiration rate $\leq$ 24/minute, heart rate $\leq$ 100/minute, and systemic blood pressure $\geq$ 90 mmHg. Although this endpoint remains unvalidated, it had been used in an earlier trial conducted by Shionogi and was agreed upon with the Review Team. The majority of subjects enrolled also received some other NAI during the study period making it difficult to draw conclusions in the subgroup of influenza-infected subjects who did not receive other NAIs (the primary analysis population). The trial enrolled from 2009 through 2012 but

ultimately was unable to show a difference between the two arms in the primary analysis population. It is not clear whether peramivir is not effective in the setting of severely ill patients or whether the endpoint used was not able to discriminate a true benefit. Given the interest in having an antiviral product that could be used in severely ill patients, the Review Team believes Study BCX1812-301 should be described in the product label in order to describe the lack of measurable benefit.

Overall, both the Statistical and Clinical reviewers concluded that the evidence submitted in the NDA persuasively demonstrated a treatment effect of peramivir. Although both peramivir 300 mg and 600 mg IV provided clinical benefit as measured by a reduction in duration of symptoms, they concluded that other endpoints provided support for the selection of the 600 mg dose for approval.

8. Safety

For a complete discussion of the safety review of this NDA, please refer to the Clinical Review performed by Dr. Peter Miele. Major safety findings from his review are summarized below.

- *Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference (if NME will be approved)*

The Applicant provided full safety data including reported clinical adverse events and results of laboratory monitoring on all subjects in Study 0722T0621 and all supportive trials. Because the exposures provided by IV and IM delivery of peramivir were similar, the safety data from cohorts receiving the same doses in trials of acute uncomplicated influenza were pooled. In this analysis, data from the four placebo-controlled trials were combined with data from Study 0815T0631, an active-controlled Japanese trial evaluating peramivir 300 mg and 600 mg compared to approved oseltamivir. This pooled analysis formed the main focus of Dr. Miele's safety review. Data from another small Japanese trial (Study 0816T0632) comparing peramivir to oseltamivir in patients considered at high risk for influenza complications was included in some of the analyses.

The safety database for the primary pooled safety analyses included 1399 subjects who received one dose of either 150 mg, 300 mg, or 600 mg of peramivir and 664 who received the proposed to-be-marketed dose of 600 mg. Information related to deaths and some other events of special interest were reviewed from the broader safety population including the supportive trials conducted in hospitalized subjects.

Overall, the clinical safety data submitted in this NDA confirmed that the dose selected could be safely administered to patients with acute, uncomplicated influenza. The major safety finding was related to localized infusion/injection reactions, primarily with the IM formulation.

Additional safety data on peramivir use was summarized by the Applicant related to post-marketing use in Japan, where peramivir was approved for treatment of influenza in 2010. Shionogi collected 407 postmarketing safety reports in 324 Japanese patients from an estimated 794,000 patients exposed to peramivir. Non-serious AEs were reported in 126 adult patients (18-94 years) and 20 patients of unreported age. Commonly reported non-serious AEs included gastrointestinal events such as diarrhea, vomiting, and nausea and other events such as rash, urticaria, and dizziness. Among the non-serious AEs not reported in the clinical trials were cases of neuropsychiatric AEs such as altered state of consciousness, loss of consciousness, abnormal behavior, delirium, and hallucinations as had been reported with other approved NAIs. Serious AEs were reported in 94 adult patients (11 with unreported age). The most commonly reported SAEs included abnormal hepatic function, shock, and anaphylactic shock (6 reports each), hemorrhagic enterocolitis (5 reports), and liver disorder and acute renal failure (4 reports each).

Three postmarketing surveillance studies were conducted by Shionogi in Japan, one in adults, one in pediatric patients, and one in patients at high risk for complications of influenza. The adult surveillance study enrolled 1,309 patients at 193 institutions in Japan, almost all treated in an outpatient setting. Of these, 51 patients (4%) experienced 78 AEs deemed related to peramivir by the prescribing physicians. The most common AEs were diarrhea, vomiting, and nausea and all reported AEs were non-serious. In the pediatric surveillance study, 1,254 patients < 15 years of age were evaluated at 173 institutions; about 10% of patients were hospitalized. Ninety-two patients experienced 115 AEs (including 14 SAEs) deemed related to peramivir by the prescribing physicians. There were five SAEs of abnormal behavior and five of neutropenia. The most common AEs included diarrhea, abnormal behavior, vomiting, and nausea. The surveillance study in high-risk patients is still ongoing but an interim report was submitted on 193 patients, almost all hospitalized, from 109 institutions. In this study, 34 patients (18%) experienced 54 AEs deemed related to peramivir by the prescribing physicians. Four SAEs were reported: viral myositis, AST increased, decreased neutrophil count, and decreased white blood cell count. Overall, AEs were reported relatively infrequently in the surveillance studies and the events reported were similar to those observed in the clinical trials with the exception of the neuropsychiatric AEs. These events have previously been described in association with other approved NAIs, although causality has not been established.

- *General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.*

Among subjects enrolled in the trials of acute, uncomplicated influenza, only a single death was reported. A 46-year-old South African female was enrolled and treated with peramivir 300 mg IM in Study BCX1812-211. She initially appeared ill with nausea, nasal congestion, myalgia, vomiting, pharyngitis, and bilateral rhonchi and her RAT was positive for influenza A. She was seen in clinic on Days 3, 5, and 9 and appeared to be improving but symptoms of nasal congestion, cough, and aches and pains persisted. On Day (b) (6) she was seen in clinic and complained of headache and vomiting and was thought to be mildly disoriented. Later that same day her condition worsened and she was hospitalized with a clinical diagnosis of meningitis. CT scan of the head reportedly showed

pansinusitis and evidence of increased intracranial pressure. Her condition deteriorated rapidly and she died. No post-mortem examination was done. The investigator assessed her death as unlikely to be related to study drug.

Twenty-seven deaths were reported in the submitted supportive trials in hospitalized subjects, including 24 in subjects receiving peramivir. Of the 24 deaths in subjects receiving peramivir, 22 occurred in the open-label Study BCX1812-303 conducted during the 2009 influenza pandemic. These deaths were reviewed but attribution to study drug was not possible as all were confounded by the subjects' severe illness and multiple comorbidities. Deaths in the open-label trial were generally attributed to progressive influenza or complications of influenza. In the two additional peramivir subjects who died in the hospitalized controlled trials, the deaths were attributed to viral myocarditis and acute respiratory distress syndrome (ARDS) with staphylococcal infection. For a more complete description of the deaths in these supportive trials, please see Section 7.3.1 of Dr. Miele's Clinical Review.

Serious adverse events (SAEs) were uncommon in the pooled trials of acute uncomplicated influenza. There were no SAEs reported in Study 0722T0621 and only one reported in a subject receiving peramivir in Study BCX1812-211 (meningitis, fatal case described above). Four subjects receiving peramivir in Study 0815T0631 experienced SAEs (asthma, influenza, myalgia, and pneumonia) compared to 2 subjects receiving oseltamivir (vomiting and bacterial pneumonia). None of the SAEs in subjects receiving peramivir were considered related to study drug.

Discontinuations of dosing due to adverse events (AEs) were not reported in the pooled trials of acute, uncomplicated influenza as these trials evaluated a single-dose regimen. About 1% of subjects enrolled in the pooled trials discontinued study follow-up because of an AE, most commonly because of rash or drug eruption. This rate of study discontinuation was comparable to the rate observed in subjects receiving oseltamivir in the pooled trials. None of the subjects receiving placebo discontinued study due to an AE.

Overall, the majority of reported AEs were considered of mild intensity. Non-serious AEs assessed as moderate or severe intensity were reported in about one quarter of subjects receiving peramivir in Study 0722T0621 and about 15% of subjects receiving peramivir in one of the other pooled trials. Most of the non-serious AEs of moderate or severe intensity were in the category of "Investigations" (i.e., laboratory or electrocardiogram abnormalities). Notable among these, in the Shionogi Studies 0722T0621, 0815T0631 and 0816T0632, 16 subjects receiving peramivir were described as having QT prolongation. A similar or higher rate of QT abnormalities was reported in subjects receiving either placebo or oseltamivir in those trials. Review of the electrocardiogram data from these trials suggests that this finding may have been an artifact caused by higher baseline heart rates in febrile subjects. Electrocardiograms were reviewed by a central study facility and most were interpreted as normal. The Applicant conducted a thorough QT study using an FDA-endorsed study design and found no significant QTc prolongation with either the proposed clinical dose (600 mg) or a supratherapeutic dose (1200 mg).

About 2% of subjects in the IM clinical trials reported AEs related to injection site reactions. These included pain or discomfort and creatinine phosphokinase elevations. These reactions are not surprising as the IM administration of a 600 mg dose required two 2-mL gluteal injections. However, injection site pain occurred at similar rates in peramivir and placebo arms. No clinically significant infusion reactions were noted with the IV formulation of peramivir.

Although the rates of SAEs and treatment discontinuations due to AEs were relatively low in the pooled clinical trials of acute, uncomplicated influenza, many subjects experienced AEs or laboratory abnormalities with lesser impact. Many of the AEs reported in the CRFs represented asymptomatic laboratory abnormalities the investigators considered clinically relevant. Of the clinical AEs reported, the most common regardless of causality were diarrhea, nausea, and dizziness. For a listing of all treatment emergent adverse events (TEAEs) occurring more frequently in subjects receiving peramivir, please see Table 3 taken from Dr. Miele's Clinical Review.

Table 3: 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)
Diarrhea	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: Abstracted from Clinical Review NDA 206426, P. Miele, page 137

[Note: In the display above, the numbers and proportions of listed laboratory abnormalities are not the same as those identified by analyzing the laboratory datasets directly as not all investigators reported laboratory abnormalities as clinical AEs in the same way. The Review Team considers the direct data analysis a more accurate method for determining the incidence of laboratory abnormalities.]

Clinically significant laboratory abnormalities occurred in a relatively small number of subjects in the clinical trials. In general, the Review Team considers it more reliable to assess laboratory abnormalities using the objective laboratory datasets and not the clinical AE datasets which depend on investigator reporting. Table 4 displays clinically relevant laboratory abnormalities (Grade 2-4, moderate, severe or life-threatening) occurring in at

least 2% of either treatment arm and observed more frequently in subjects receiving peramivir 600 mg (IV or IM) than placebo. A similar table will be displayed in the product label.

Table 4: Laboratory Abnormalities Occurring in ≥2% of Subjects Treated with RAPIVAB 600 mg

Laboratory Parameter Abnormality[a]	RAPIVAB 600 mg	Placebo
Alanine Aminotransferase (> 2.5 x ULN)	(N= 654) 3%	(N=430) 2%
Serum Glucose (> 160 mg/dL)	(N=660) 5%	(N=433) 3%
Creatine Phosphokinase (≥ 5.9 x ULN)	(N=654) 4%	(N=431) 2%
Neutrophils (< 1 x10^9/L)	(N=654) 8%	(N=430) 6%

[a]Frequencies based on treatment-emergent laboratory abnormalities

Safety data from the randomized, placebo-controlled Study BCX1812-301 was also reviewed as part of the Clinical Review. Overall, subjects in the trials of severe influenza requiring hospitalization experienced higher rates and more severe AEs and SAEs than those with uncomplicated influenza. The reported SAEs were consistent with events expected in severely ill, hospitalized subjects (e.g., bacterial infections/sepsis, ARDS, confusion, multi-organ disorder, etc.). Often these cases were confounded as subjects had significant comorbidities that made interpretation of the events and the relationship to peramivir difficult. However, the safety profile in hospitalized subjects was consistent with that observed in the less ill population and the rates of specific AEs were comparable between subjects receiving peramivir and those receiving placebo. In a subset of 101 subjects with serious influenza requiring hospitalization treated with peramivir 600 mg alone, the following adverse reactions were also reported: constipation 4%, insomnia 3%, AST increased 3%, and hypertension 2%.

- *Immunogenicity*

As peramivir is a well-characterized small molecule with no biologic components, there are no concerns regarding immunogenicity.

- *Special safety concerns*

Based on either the peramivir development program or known safety signals with approved NAIs, a number of specific AEs were evaluated in individual trials and the pooled safety database. Among the AEs of special interest identified in reviews of other NAIs were neuropsychiatric events, rash, hypersensitivity, liver enzyme elevations, and hemorrhagic colitis. As not all of these AEs were identified in the peramivir safety review,

not all will be discussed in this CDTL Review. For a full discussion of all evaluated AEs of special interest, refer to Section 7.3.5 Submission Specific Primary Safety Concerns in Dr. Miele's Clinical Review.

As noted in the Clinical Review, Standard MedDRA Queries (SMQs) of broad or narrow terms were used to identify special safety concerns in patients receiving peramivir. The only SMQs that demonstrated at least a 2% risk difference between peramivir and placebo were those of "leukopenia" and "haematopoietic cytopenias" which were both driven by the AEs reported as "neutrophil count decreased." Assessment of complete laboratory data suggested this as a potential safety signal as decreases in neutrophil values were documented in 8% of subjects receiving peramivir compared to 6% of those receiving placebo (see Table 3). The clinical events of leukopenia and neutropenia were generally not serious.

Neuropsychiatric events have been associated with NAIs in postmarketing spontaneous reports although causality has never been established. First oseltamivir, then later zanamivir, was labeled with warning language regarding the occurrence of abnormal and potentially self-injurious behavior, particularly in pediatric patients. The peramivir clinical trials monitored for these events and the Applicant provided a summary of Japanese postmarketing AE reports. The FDA analysis included both broad and narrow SMQ terms to evaluate this controversial safety issue is shown in Table 5 below, taken from Dr. Miele's Clinical Review. None of these AEs were reported to be serious.

Table 5: 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: Abstracted from Clinical Review NDA 206426, P. Miele, page 130

As noted in the Clinical Review, "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." Because neuropsychiatric events have been reported in postmarketing cases (mostly from Japan) related to other NAIs and postmarketing cases have been reported with peramivir, precautionary language similar to that in other NAI labels will be included in the peramivir label.

Neurologic events such as seizures were also evaluated during the safety review. Seizures were reported in Study BCX1812-303, a study that enrolled subjects with severe influenza illness and significant multi-system dysfunction. Two subjects in this trial experienced seizure AEs. Both subjects had respiratory failure requiring ICU care and mechanical ventilation prior to receiving peramivir and the seizures occurred in the setting of many confounding events and comorbidities. In addition, postmarketing cases reported from Japan have documented seizures in both adult and pediatric patients, usually accompanied by high fever. To date, the available data do not suggest a causative link between the occurrence of seizures and peramivir use.

Severe cutaneous reactions such as Stevens-Johnson syndrome or erythema multiforme have been reported following use of approved NAIs. A search of the pooled clinical trials for rash-related events identified a low frequency of reports among subjects receiving peramivir but numerically greater than reported among subjects receiving oseltamivir or placebo. No specific rash event was identified with increased frequency and no serious cutaneous reactions occurred during the clinical trials of uncomplicated influenza. One case described as mild, non-serious erythema multiforme was reported in a patient enrolled in the open-label study of influenza requiring hospitalization (BCX1812-303). One case of Stevens-Johnson and two cases of exfoliative dermatitis were reported as an SAE in postmarketing use of peramivir in Japan. Overall, rash events do not appear to be common with peramivir use but the pattern of skin reactions is consistent with other NAIs. The potential for skin reactions will be described in labeling.

During the peramivir development program, the FDA received safety reports related to possible hepatic dysfunction and requested an integrated safety assessment from the Applicant. In addition, the Japanese product label for peramivir (Rapiacta) describes hepatic dysfunction and jaundice as possible adverse drug reactions. Analysis of hepatic/biliary SMQs identified a risk difference between peramivir and placebo of < 1%. Review of laboratory data suggested a small increase in rate of elevated ALT among peramivir subjects compared to placebo subjects (see Table 3). There were no cases meeting Hy's Law criteria in subjects enrolled in the trials of acute, uncomplicated influenza. Overall, hepatic toxicity does not appear to represent a significant risk with peramivir.

Renal toxicity identified in early animal (rabbit) toxicology studies prompted a thorough analysis of possible renal effects of peramivir in the clinical trials. Very few clinical AEs

were identified during this review. Two subjects in Study BCX1812-212 were reported to have Grade 4 "renal impairment" requiring IV fluids and Grade 1(mild) "renal failure," respectively. Four subjects (0.6%) receiving peramivir 600 mg had documented elevations in creatinine (Grades 1-4) compared to 2 (0.3%) receiving 300 mg, 1 (0.3%) receiving oseltamivir, and 2 (0.5%) receiving placebo. Proteinuria at least Grade 2 (2+-3+) was observed in a larger number of subjects: 28 (5%) subjects receiving 300 mg peramivir, 27 (4%) subjects receiving 600 mg, 25 (7%) subjects receiving oseltamivir, and 22 (5%) subjects receiving placebo. Overall, there was no indication of significant renal toxicity in subjects enrolled in trials of acute, uncomplicated influenza.

- *Discussion of primary reviewer's comments and conclusions*

The primary Clinical Reviewer and primary Statistical Reviewer both concluded that a single dose of peramivir 600 mg IV was effective in reducing the symptoms of acute, uncomplicated influenza. The Clinical Reviewer considered the safety profile acceptable when peramivir was used in this setting.

- *Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed*

There were no substantive disagreements between the CDTL and the Review Team.

- *Discussion of notable safety issues (resolved or outstanding)*

The Applicant also summarized peramivir safety reports from the U.S. collected during the EUA during the 2009 influenza pandemic. EUA usage of peramivir was generally requested for critically ill hospitalized patients and the AEs reported reflect this population's extensive comorbidities and concomitant medications. FDA reviewers in the Division of Antiviral Products and the Office of Surveillance and Epidemiology reviewed all safety reports submitted to the FDA Adverse Event Reporting System (FAERS) during the EUA distribution of peramivir for the 2009 pandemic. Their findings were published and can be referenced for a detailed description of the peramivir EUA safety profile (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).

After careful review of the submitted data from clinical trials, postmarketing reports, and EUA use there are no unresolved safety issues. Safety signals related to serious skin reactions and neuropsychiatric events will be described in the Warnings and Precautions section as they are in other approved NAI labels.

9. Advisory Committee Meeting

An Advisory Committee was not considered warranted as peramivir is the third drug in its class to be reviewed. Safety and efficacy were considered similar to the currently approved neuraminidase inhibitors.

10. Pediatrics

The Applicant's Japanese partner (Shionogi) conducted Study 0918T0633, a single arm, open-label clinical trial of IV peramivir in 117 pediatric patients from 28 days to < 16 years of age. Subjects with a positive RAT and within 48 hours of the onset of symptoms received a single dose of 10 mg/kg IV (up to maximum dose of 600 mg). The results of this trial were submitted as supportive safety data but BioCryst has not requested any pediatric labeling. In general, the uncontrolled study design of Study 0918T0633 makes it difficult to draw conclusions regarding either the safety or efficacy of peramivir in this population. Overall, however, the safety profile of peramivir observed in the Japanese pediatric study was similar to that observed in adult subjects. In addition, some pediatric patients were allowed to enroll in Studies BCX1812- 301 and -303 evaluating severe influenza in hospitalized patients and pediatric patients were included in those allowed to receive peramivir under the conditions of the EUA. None of these uncontrolled data provide sufficient evidence of safety or efficacy in the pediatric population and the Applicant will be asked for additional data in this age group.

- *A brief documentation of the scientific data supporting extrapolation if extrapolation from one population to anther is used to support efficacy.*

In general, efficacy of influenza antiviral drugs is based on a partial extrapolation approach. Previous applications for influenza antiviral drugs have relied on one adequate and well-controlled clinical trial of treatment in pediatric patients in at least one age group with supporting safety and clinical pharmacology data in other pediatric age groups. Both Tamiflu and Relenza received extended indications for prophylaxis of influenza to pediatric age groups on the basis of inclusion of these patients in trials of household exposure or post-exposure prophylaxis.

During the development of peramivir, the Applicant argued that a placebo controlled clinical trial of influenza treatment in pediatric patients was no longer possible because the CDC recommends treatment with antiviral drugs for many children. They also note that the FDA's guidance document describing development of influenza drugs recommends against active control trials designed to show noninferiority of a new drug. (b) (4) [redacted] we have recommended the Applicant consider conducting a controlled trial comparing peramivir to one of the approved NAIs.

- *Peds exclusivity board review*

At the time of this NDA review the Applicant has not submitted a PPSR and a Written Request for pediatric studies has not been issued.

- *PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment*

The Applicant submitted their proposed pediatric plan as part of the NDA and requested a deferral of pediatric studies. Their proposal was discussed with the FDA Pediatric Review Committee on August 13, 2014. The PeRC agreed with the Review Team that a partial extrapolation of efficacy from adult trials with additional PK and safety data in pediatric patients may be a reasonable approach for pediatric development. The PeRC noted that an active control trial would allow a more informative review of safety of peramivir in pediatric patients (b) (4) The PeRC agreed with the Review Team's recommendation to grant a deferral in all pediatric age groups and agreed to the proposed timeline for studies.

A PMR for pediatric studies will be triggered under the Pediatric Research Equity Act (PREA) at the time peramivir is approved. The specific language for this PREA PMR has not been determined.

11. Other Relevant Regulatory Issues

No substantive regulatory issues remain to be resolved other than the requirement to successfully complete all facility inspections.

Clinical site inspections were conducted by the Office of Scientific Investigations. Shionogi's Study 0722T0621 was inspected in 2009 as part of the preparation for issuing the EUA. In addition, five clinical sites participating in the BioCryst-sponsored Studies BCX1812-211 and BCX1912-212 were inspected during this review cycle. One of these sites was found to have significant deficiencies related to retention of study records. As a result of this finding, the efficacy analysis was conducted with this site's data excluded. Removal of the subjects from this site had no significant impact on either the efficacy or safety analysis.

The Applicant submitted financial disclosure information for the trials determined to comprise the pivotal trials, Studies 0722T0621, BCX1812-211, BCX1812-212, and BCX1812-311. No financial conflicts of interest were identified among the 93% of investigators for whom complete data were available.

No other disciplines were consulted during this NDA review.

12. Labeling

Final decisions related to labeling remain under negotiation at the time of this CDTL Review but highlights of labeling discussions and areas of interest are addressed below.

- *Proprietary name*

The proprietary name Rapivab was proposed initially in 2010 and determined to be "conditionally acceptable." With the NDA submission, the Applicant formally proposed Rapivab and this proprietary name was reviewed by the Division of Medication Error Prevention and Risk Management (DMEPA) and found to be acceptable. The Applicant was notified of the name approval on March 6, 2014.

- *Address important issues raised by brief discussion of OPDP and OSE comments*

To date, no important safety issues have been raised by either OPDP or OSE. Both groups have been advised that peramivir will be indicated for treatment of acute, uncomplicated influenza but because it has an IV formulation, it will undoubtedly be used in the setting of hospitalized patients. The product label will clearly state that no treatment benefit was observed in the randomized, controlled trial of peramivir in hospitalized subjects.

- *Physician labeling*

The Package Insert was reviewed by staff from the Labeling group of the Study Endpoints and Labeling Development (SEALD) team who provided advice on format and content of the package insert. SEALD labeling recommendations were incorporated into the Review Team's labeling recommendations and forwarded to the Applicant.

Labeling issues on which it was most difficult to reach agreement with the Applicant included the wording of the Indications and Usage section, the placement and description of Study BCX1812-301 in hospitalized patients, the description of resistance substitutions, and the need to adjust dosing in patients with moderate or severe renal impairment. FDA Review Team proposed language for some of these key sections of the label is included below (underlined).

The Review Team agreed with the primary statement of the peramivir indication but proposed Limitations of Use in addition to the primary indication as follows:

1 INDICATIONS AND USAGE

RAPIVAB (b) (4)

Limitations of Use:

- 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 virus 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)]*.
- The efficacy of RAPIVAB could not be established in patients with serious influenza requiring hospitalization *[see Clinical Studies (14.2)]*.

After discussion with the SEALD team, the Review team recommended including a description of Study BCX1812-301 in Section 14 Clinical Studies. This text will include a short description of the study design and primary endpoint and a clear statement that the trial failed to show a difference between peramivir and placebo. A statement regarding lack of efficacy is also included in the Indications Limitations of Use (see above). The Review Team also recommended that a statement be included in Section 8 Specific Populations section referring to the study description in Section 14. The following language was proposed to the Applicant:

8.7 Patients with Serious Influenza Requiring Hospitalization

The use of RAPIVAB was not shown to provide benefit in patients with serious influenza requiring hospitalization (b) (4)
[see Indications and Usage (1) and Clinical Studies (14.2)].

14.2 Serious Influenza Requiring Hospitalization

The efficacy of RAPIVAB has not been established in patients with serious influenza requiring hospitalization *[see Indications and Usage (1)]*. (b) (4)

A randomized, double-blind, multicenter, placebo-controlled trial (Study 301) was conducted in 398 subjects with serious influenza requiring hospitalization. (b) (4) The primary endpoint was time to clinical resolution defined as the time in hours from initiation of study treatment until resolution of at least 4 of 5 signs (temperature, oxygen saturation, respiration rate, heart rate, or systolic blood pressure), maintained for at least 24 hours. RAPIVAB plus standard of care did not improve median time to clinical resolution compared with standard of care alone.

As noted in Section 5 of this CDTL Review, the Clinical Pharmacology team (b) (4) The Applicant could not provide adequate safety data for patients with exposures as high as those achieved in patients with moderate or severe renal

impairment. Therefore, we proposed the following dosing recommendations be included in Section 2 Dosage and Administration with the explanatory PK information included in Section 12 Clinical Pharmacology:

2.2 Dosing in Patients with Renal Impairment

Significantly increased drug exposures were observed when RAPIVAB was administered to subjects with renal dysfunction *[see Clinical Pharmacology (12.3)]*. Therefore, the RAPIVAB dose should be reduced for patients with baseline creatinine clearance below 50 mL/min using the recommendations in Table 1. No dose adjustment is required for single administration of RAPIVAB in patients with creatinine clearance of 50 mL/min or higher *[see Clinical Pharmacology (12.3)]*.

In patients with chronic renal impairment maintained on hemodialysis, RAPIVAB should be administered after dialysis at a dose adjusted based on renal function (Table 1) *[see Clinical Pharmacology (12.3)]*.

Table 1. Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance* (mL/min)		
	≥50	**30-49**	**10-29**
Recommended Dose (mg)	600	200	100

* Calculated using the Cockcroft and Gault equation.

12.3 Pharmacokinetics

Patients with Impaired Renal Function: A trial was conducted in subjects with various degrees of renal impairment. When compared to a concurrent cohort with normal renal function, no change in mean C_{max} was observed (6 subjects per cohort). However, mean $AUC_{0-\infty}$ after a single 2 mg/kg IV dose was increased by 28%, by 302%, and by 412% in subjects with creatinine clearance 50-79, 30-49, and 10-29 mL/min, respectively.

Hemodialysis was effective in reducing systemic exposure of peramivir by 73% to 81%.

Due to the marked increase in peramivir exposure ($AUC_{0-\infty}$) in subjects with creatinine clearance less than 50 mL/min, a dose reduction is recommended for these patients. No dose adjustment is required for patients with creatinine clearance 50mL/min or higher *[see Dosage and Administration (2.2)]*.

The Virology Reviewer requested inclusion of a number of NAI resistance-associated substitutions in the Resistance and Cross Resistance subsections of Section 12.4 Microbiology not previously included by the Applicant. The goal is to display all known resistance substitutions, regardless of the source of their identification (i.e., not only from

the Applicant's cell culture studies or clinical trials). The specific substitutions and the method of displaying them in the product label are still under discussion.

The Applicant proposed including descriptions of serious skin reactions, neuropsychiatric events, and risk of serious bacterial infections in Section 5 Warnings and Precautions. These issues are also included in other approved NAI labels and the Review Team agreed with the Applicant's proposal with minor revisions to the proposed language as shown below:

> ***5.1 Serious Skin/Hypersensitivity Reactions***
> Rare cases of serious skin reactions, including erythema multiforme, have been reported with RAPIVAB in clinical studies and in postmarketing experience. (b) (4) Stevens-Johnson syndrome has been reported with RAPIVAB 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 (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.
>
> ***5.3 Risk of Bacterial Infections***
> There is no evidence for efficacy of RAPIVAB in any illness caused by agents other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. RAPIVAB has not been shown to prevent such complications. Prescribers should be alert to the potential for secondary bacterial infections and treat with antibiotics as appropriate.

- *Highlight major issues that were discussed, resolved, or not resolved at the time of the CDTL review.*

In addition to the issues described in the labeling discussion above, another major issue that has been discussed but not resolved is the relative effectiveness of peramivir in influenza B infection. None of the clinical trials of peramivir in acute, uncomplicated influenza enrolled an adequate number of subjects with influenza B to determine clinical efficacy. Cell culture and animal model data suggest that peramivir should have antiviral

activity against influenza B but that activity may be less robust than for influenza A. This is not a novel problem in influenza antiviral drug development as other approved NAIs also had relatively small numbers of subjects with influenza B enrolled in clinical trials at the time of initial approval. The Review Team will recommend issuing a Postmarketing Commitment requesting more dedicated study of naturally-acquired influenza B infection and how such a study might be accomplished. For the proposed labeling, the Review Team decided to leave the primary indication statement inclusive ("treatment of acute uncomplicated influenza") without reference to virus type. The lack of data in influenza B infection will be addressed in the Limitations of Use statement and in other sections of the label as appropriate.

- *Carton and immediate container labels (if problems are noted)*

The carton and immediate container labels were evaluated by staff from DMEPA. A number of recommendations were sent to the Applicant to improve readability and prominence of important information. The Applicant responded adequately to these recommendations.

- *Patient labeling/Medication guide (if considered or required)*

As peramivir is intended as an IV injection, patients will not be self-administering drug. Therefore, no patient labeling is proposed.

13. Recommendations/Risk Benefit Assessment

- *Recommended Regulatory Action*

I concur with the conclusions of the multi-disciplinary FDA Review Team and recommend this NDA for peramivir (Rapivab) for injection be approved for the treatment of acute, uncomplicated influenza in adults who have been symptomatic for less than 2 days. The regimen recommended for approval is a single dose of 600 mg administered via IV infusion over 15 to 30 minutes.

The submitted pivotal clinical trial Study 0722T0621 met the regulatory standards for accepting a single adequate and well-controlled clinical trial to support approval. The trial design was rigorous, including multiple clinical sites, randomization, a carefully selected population, and blinded comparison to a placebo control. Both doses of peramivir were shown to provide faster alleviation of pre-specified symptoms of influenza compared to placebo; the primary efficacy results were consistent across subgroups and were supported by secondary endpoints. Both the Statistical and Clinical Reviewers concluded the efficacy results were statistically very persuasive. Although both 300 mg and 600 mg doses demonstrated clinical benefit, the 600 mg dose provided better virologic activity. In addition, supportive data was provided from three other clinical trials of IM peramivir in subjects with acute, uncomplicated influenza and additional information from clinical trials in other populations was reviewed primarily to characterize the safety profile.

Although there are no remaining issues from any review discipline that would preclude approval of peramivir, the recommendation for approval is contingent on successful completion of all pending facility inspections and resolution of the identified GMP deficiencies. At the time of writing this CDTL Review, BioCryst and its sole drug product manufacturing site have not resolved critical inspection issues and approval may not be possible.

- *Risk Benefit Assessment*

The data submitted with this NDA provided evidence that peramivir provided clinical, and possibly virologic, benefit in patients with acute uncomplicated influenza. Using a patient-reported outcome endpoint similar to one used for previous influenza antiviral drugs, the Applicant demonstrated that peramivir doses of either 300 mg or 600 mg reduced the time to alleviation of a constellation of influenza-associated symptoms compared to placebo. All seven influenza symptoms were reduced to absent or mild in intensity about 1 day sooner in subjects receiving peramivir and overall return to usual activities occurred 1 to 2 days sooner. Although, this may not sound like a blockbuster improvement for a usually self-limited illness, one must remember the size of the population who may benefit and the magnitude of effects on a community during annual influenza epidemics.

In addition, the peramivir trials demonstrated that use of the drug led to reductions in viral shedding. The trials were not designed to assess transmission of influenza but it is virologically plausible to assume that reduced viral shedding may lead to reduced transmission. The available virologic data did identify emergence of a known influenza A H1N1 resistance substitution in neuraminidase (H275Y) in a small number of clinical trials subjects receiving peramivir. Substitutions in hemagglutinin were also identified but the clinical implications of these are less well understood. In general, the rates of resistance were low.

Overall, the safety profile of peramivir was acceptable. Serious adverse reactions were very uncommon in the clinical trials and the most common non-serious adverse events were observed at similar rates in peramivir and placebo recipients. Because the treatment is a single dose, no one discontinued treatment prematurely; adherence to treatment can be assured. Adverse reactions associated with other NAIs were evaluated in the peramivir safety database including the postmarketing experience in Japan and the U.S. EUA experience. As noted with other approved NAIs, a small number of cases of serious skin reactions and neuropsychiatric events were reported with use of peramivir, primarily from postmarketing reports. These uncommon events will be addressed in labeling with Warnings and Precautions language similar to that found in other NAI labels.

Treatment of influenza (in addition to routine vaccination) has long been considered part of the public health armamentarium because of the favorable community level risk-benefit assessment. The ultimate public health goal is to reduce the number of influenza-related deaths or serious complications. The Applicant submitted data from a large randomized, placebo-controlled trial of peramivir in subjects with severe influenza requiring

hospitalization. Unfortunately, this study failed to show a treatment benefit of peramivir based on an endpoint of time to clinical stability, defined as normalization of at least 4 of 5 clinical signs (oral temperature ≤ 37.2°C, oxygen saturation ≥ 92%, respiration rate ≤ 24/minute, heart rate ≤ 100/minute, and systemic blood pressure ≥ 90 mmHg). As no other influenza antiviral drug has been approved for use in severely ill hospitalized patients, it is not clear whether the lack of efficacy of peramivir in this setting is due to a failure of the drug or a failure to measure an adequately discriminating endpoint.

Peramivir is the first influenza antiviral drug available as an IV formulation. While this may limit use of the drug to settings such as large clinics and offices or hospital emergency departments, there is clearly a niche for an IV antiviral even for the indication acute, uncomplicated influenza. The single dose regimen will allow clinical care facilities to diagnose patients with influenza and immediately offer a complete treatment course. Patients who feel ill with influenza may appreciate the option of a single-dose regimen that does not require a trip to the pharmacy. As noted above, the single dose of peramivir for treatment ensures adherence to the antiviral regimen that may have a positive impact on transmission. Undoubtedly, clinicians will be tempted to use peramivir in the setting of more severely ill hospitalized patients who may need an IV therapy in spite of the lack of proven efficacy. Although peramivir failed to show efficacy in the clinical trial of hospitalized subjects, the drug appeared to be safe in that population.

In summary, a single dose of peramivir 600 mg provided clinical benefit as measured by time to alleviation of a constellation of influenza symptoms compared to placebo in patients symptomatic for less than 2 days. The safety profile is acceptable with no serious safety risks identified. The Applicant has provided sufficient data to determine the risk-benefit assessment is favorable for peramivir as treatment for acute, uncomplicated influenza.

- *Recommendation for Postmarketing Risk Evaluation and Management Strategies*

Based on the review of all material submitted with this NDA and in consultation with our colleagues in DRISK, a REMS will not be required for peramivir.

- *Recommendation for other Postmarketing Requirements and Commitments*

A pediatric PMR will be required under PREA as described in Section 10. The specific language of the PMR has not been decided but it will include the following elements:

> Conduct a clinical trial to evaluate the pharmacokinetics, safety, and antiviral activity of peramivir administration in pediatric subjects with acute uncomplicated influenza infection from birth to less than 18 years of age. Include characterization of peramivir resistance-associated substitutions in viral isolates from subjects with prolonged viral shedding.

The Applicant will also be asked to submit additional clinical data from subjects with influenza B virus infection and evaluate peramivir use in other at-risk patient populations considered likely to receive the drug off-label. Draft proposed PMCs include:

> Submit clinical data from an adequate number of subjects to characterize the effectiveness of peramivir administration in patients with acute uncomplicated influenza B virus infection. These data may be collected from the pediatric study required under PREA or from a new stand-alone clinical trial in a different population. Conduct genotypic resistance analysis of neuraminidase and hemagglutinin using samples directly from subjects without an intervening culture step. Conduct phenotypic analysis, including cross-resistance to approved neuraminidase inhibitors.
>
> Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in elderly subjects aged 65 years or older with influenza infection.
>
> Conduct a clinical trial to evaluate the pharmacokinetics, safety and antiviral activity of peramivir administration in a predominantly ambulatory setting in subjects with influenza infection at higher risk for influenza complications, as defined by the recommendations of the (b) (4)

Additional virology data will be requested to fully characterize resistance to peramivir and the possible impact of substitutions in the hemagglutinin gene on antigenicity. Draft proposed language for these PMRs/PMCs is as follows:

> Submit the remainder of the clinical resistance data that were not included with the NDA. These include both the HA and NA data for studies BCX1812-201, BCX1812-211, and BCX1812-311.
>
> Determine the cross-resistance to oseltamivir and zanamivir for all of the HA peramivir resistance substitutions that have yet to be evaluated (A/H1N1 HA D129S, R208K; A/H3N2 HA G78D, K189E; B HA T139N, G141E, R162M, D195N, T197N, Y319H). Additionally, determine cross-resistance to oseltamivir/zanamivir resistance substitutions (A/H1N1 NA R152K, I122K/T, G248R+I266V, Q312R+I427T, R371K, A/H3N2 NA E41G, I222L/V, Q226H, S247P, HA A28T, K68R, E114K, R124M, N145S, S165N, S186F, N199S, K222T, B NA D198Y, A246D/S/T, G420S).
>
> Evaluate the impact of peramivir resistance-associated substitutions in hemagglutinin (HA) on the effectiveness of influenza vaccine in cell culture assays:
> - Titrate the neutralization and hemagglutinin inhibition activity of the serum samples from multiple subjects vaccinated with the influenza virus vaccine against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus. A titration of the serum samples should be

evaluated using established methods for determining hemagglutination inhibition (HI) as well as virus neutralization (e.g. plaque number reduction or % infected cells based on nuclear NP staining). We recommend performing neutralization assays using different input concentrations of virus to confirm that assay conditions are such that the EC50 value is independent of virus concentration.

- Titrate the neutralization and hemagglutinin inhibition activity of the baseline and end of treatment serum samples from multiple subjects treated with peramivir against recombinant virus with the peramivir resistance substitutions in the HA and their parental virus.
- Compare the antigenicity of wild type (WT) and HA mutants, selected during peramivir treatment in cell culture, against immune serum (convalescent or vaccine-induced) from human subjects and from animal models vaccinated with inactivated WT virus. Antigenicity should be determined using both HI and neutralization assays.

- *Recommended Comments to Applicant*

  No additional comments need to be conveyed to the Applicant.

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

/s/

LINDA L LEWIS
11/07/2014