CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206426Orig1s000

SUMMARY REVIEW

Decisional Review for NDA 206426

Date	December 1, 2014
From	Debra Birnkrant, M.D.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	NDA 206426/Original Submission
Applicant Name	BioCryst Pharmaceuticals, Inc.
Date of Submission	December 23, 2013
PDUFA Goal Date	December 24, 2014
Proprietary Name / Established (USAN) Name	Rapivab™ /peramivir
Dosage Forms / Strength	200 mg (20 mL) vial; 600 mg single dose administered by intravenous (IV) infusion for a minimum of 15 minutes
Proposed Indication(s)	Indicated for the treatment of acute uncomplicated influenza in adults 18 years and older
Action/Recommended Action for NME:	*Approval pending satisfactory manufacturing inspections*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Peter Miele, M.D.
Statistical Review	Greg Soon, Thomas Hammerstrom, Dionne Price
Pharmacology Toxicology Review	Dr. Kuei-Meng Wu, supervised by Dr. Hanan Ghantous.
CMC Review/OBP Review	Drs. Fuqiang Liu, Banu Zolnik, Biopharmaceutics and Neal Sweeney, Product Quality Microbiology. Dr. Krishna Ghosh conducted the review for Compliance. Dr. Stephen Miller served as CMC-Lead.
Microbiology Review	Takashi Komatsu, Ph.D.,RAC and Eric Donaldson,Ph.D. who conducted the review of virology and resistance data, with supervisory concurrence by Jules O'Rear, Ph.D..
Clinical Pharmacology Review	Leslie Chinn, Ph.D. and Jeffry Florian, Ph.D. with secondary review provided by Islam Younis, Ph.D.
DDMAC	Oluwaseun Asante, Pharm.D.
DSI	Antoine El Hage, Ph.D.
CDTL Review	Linda Lewis, M.D.

OSE/DMEPA	James Schlick, RPh, MBA
OSE/DDRE	
OSE/DRISK	Robert G. Pratt, Pharm.D., George Neyarapally, Pharm.D., M.P.H.
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

This Division Director's memorandum provides a topline summary of NDA 206426 for BioCryst Pharmaceuticals', Inc. New Drug Application (NDA) for an intravenous formulation of peramivir, an influenza neuraminidase inhibitor for treatment of adult patients with acute uncomplicated influenza. This decisional review summarizes pertinent findings from the original NDA submission and FDA's multidisciplinary reviews and product labeling.

2. Background

Seasonal influenza is a respiratory infection caused by viruses that belong to the Orthomyxoviruses family of RNA viruses. Typical symptoms include: fever or feverishness, chills, cough, sore throat, nasal congestion, myalgias, headache and fatigue. Though it can be a self-limited disease, there can be serious complications such as bacterial pneumonia, sinusitis and otitis media. Regarding severity, CDC estimates the number of flu-associated deaths in the U.S. over a 30-year period between 1976-2006, to range from 3,000 to up to 49,000 per year. Further, as another assessment of severity, U.S. hospitalization rates are estimated at 200,000 hospitalizations per year.

There are two classes of approved antivirals that are used for treatment and prophylaxis of acute uncomplicated disease, neuraminidase inhibitors and adamantanes. Tamiflu (oseltamivir) and Relenza (zanamivir) are both neuraminidase inhibitors that are approved for treatment of acute uncomplicated disease in adults and children who have been symptomatic for no more than 2 days, as well as influenza prophylaxis. Treatment effects in controlled clinical trials showed about a 1-day improvement in time to alleviation of a constellation of symptoms rated as "none" or "mild" including: nasal congestion, sore throat, headache, aches, chills, etc. Older drugs that belong to the adamantane class are not presently recommended for use by CDC for the currently circulating strains because of resistance and lack of activity against influenza B virus. Notably, there are no approved drugs for serious, hospitalized influenza.

The NDA for the peramivir was submitted on December 23, 2013 and reviewed under the PDUFA V program. For a complete regulatory history of the application see the clinical review by Dr. Peter Miele and Dr. Linda Lewis' CDTL memorandum.

Peramivir is the third drug in the neuraminidase class and is recommended for use in adult patients with acute uncomplicated illness based primarily on data from the four placebo-controlled Phase 2 or 3 trials in adults with acute uncomplicated influenza, including Studies 621, 211, 212, and 311 that are excerpted in tabular format below from Dr. Miele's clinical review.

Placebo-Controlled Phase 2 and 3 Clinical Trials of Peramivir

Study ID	Population	Study Design	Peramivir Dosage	# Subjects Randomized/ Treated	Role in NDA
Phase 2/3 Trials in Acute Uncomplicated Influenza – Placebo-Controlled					
0722T0621	Adults w/ uncomplicated acute influenza	Phase 2 double-blind, placebo-controlled, parallel group, comparative dose-finding	300 mg or 600 mg IV single dose	Peramivir 300 mg IV 99/99 Peramivir 600 mg IV 100/99 Placebo 101/100	Pivotal
BCX1812-211	Same as above	Phase 2 randomized, double-blind, placebo-controlled	150 mg or 300 mg IM single dose	Peramivir 150 mg IM 114/113 Peramivir 300 mg IM 115/115 Placebo 115/114	Supportive
BCX1812-311	Same as above	Phase 3 randomized, double-blind, placebo-controlled	300 mg IM single dose	Peramivir 300 mg IM 57/57 Placebo 25/25	Supportive
BCX1812-212	Same as above	Phase 2 randomized, double-blind, placebo-controlled	600 mg IM single dose	Peramivir 600 mg IM 202/200 Placebo 203/202	Supportive

The original NDA submission also contained data from other clinical trials in acute uncomplicated influenza that were not placebo-controlled and in hospitalized patients with influenza as well as one pediatric trial. Integrated safety analyses conducted by Dr. Miele were based on all Phase 2/3 trials, safety summaries from Phase 1 trials in healthy volunteers, and postmarketing data from foreign sources since peramivir is approved in other countries. The analysis of efficacy, conducted in collaboration with Dr. Thomas Hammerstrom, Biometrics, was based chiefly on data from the Shionogi Study 621, with supplemental data from Studies 211, 212, 311, and 631, an oseltamivir-controlled trial in adults with acute uncomplicated influenza.

Dr. Leslie Chinn, Clinical Pharmacology, reviewed the BioCryst Phase 1 Studies 111 and 113 that demonstrated the bioequivalence of the IM and IV peramivir formulations. Although the Applicant submitted a clinical trial evaluating a dose of peramivir 10 mg/kg IV in Japanese pediatric patients, the Clinical Pharmacology Team did not review these data in detail because a pediatric indication was not being requested.

Per Dr. El-Hage, Office of Scientific Investigations (OSI), FDA inspected three clinical sites that participated in Shionogi Study 621, as well as Shionogi headquarters and the Contract Research Organization (CRO) that conducted the trial as part of the review process for the 2009 Emergency Use Authorization for peramivir for treatment of pandemic influenza. No major observations resulted from these inspections. In addition, five clinical trial sites that participated in trials 211 and 212 were inspected. Based on the inspection findings, the data generated at four of the five clinical sites were found to be reliable and acceptable in support of this application.

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

3. CMC/Device

The CMC reviewers of the peramivir NDA are: Drs. Fuqiang Liu, Banu Zolnik, Biopharmaceutics and Neal Sweeney, Product Quality Microbiology. Dr. Krishna Ghosh conducted the review for Compliance. Dr. Stephen Miller served as CMC-Lead. The CMC team reviewed data to assure the identity, strength, purity, sterility and quality of IV peramivir. Although stability data provided by the Applicant are adequate to support an expiry date of 60 months, the CMC review team could not recommend approval because the overall recommendation for the manufacturing and testing facilities is pending. According to Dr. Liu's review, the only drug product manufacturer, (b) (4) was classified as OAI, and the Office of Compliance is considering a Withhold determination for this facility. This NDA cannot be approved until the (b) (4) issues have been resolved and an overall recommendation of Acceptable is made for the establishment. Alternatively, the Applicant could select a different drug product manufacturer and submit appropriate information to the NDA (e.g., sterility assurance controls and data), but this approach would exceed the PDUFA goal date.

4. Nonclinical Pharmacology/Toxicology:

Please see review of submitted nonclinical toxicology studies by Dr. Kuei-Meng Wu, supervised by Dr. Hanan Ghantous.

Per Dr. Wu's review, the nonclinical safety profile of peramivir has been evaluated in: in vitro and in vivo pharmacokinetic studies; safety pharmacology studies assessing effects on the CNS, cardiovascular, respiratory, gastrointestinal and renal systems; single-dose IV toxicity studies in three species; repeat-dose IV toxicology studies in rats and monkeys up to one-month duration; reproductive IV toxicity studies in rats and rabbits; in vitro and in vivo mutagenicity assays that showed that peramivir was not mutagenic or clastogenic; and juvenile studies in rats, nephrotoxicity assessment in rabbits and antigenicity studies in guinea pigs. Carcinogenicity studies by IV injection of peramivir were not performed. However, in an oral carcinogenicity study in Sprague-Dawley rats, no drug-related neoplasms were observed at drug exposures 0.2 ~ 0.5-fold that of humans at the clinically recommended dose of 600 mg/day.

Other results from safety studies include the following:

- Single-dose toxicity studies conducted in rats, mouse and monkeys revealed that IV and IM routes of administration caused local irritation.

- In the rabbit, the kidney was identified as the target organ of toxicity after single and multiple doses. A single-dose **oral** study in rabbits elicited renal toxicity including discolored foci in the kidneys, without microscopic changes, at 2400 mg/kg, whereas a single **IV** dose at 200 or 300 mg/kg produced renal tubular necrosis accompanied by an increased BUN, creatinine, urine volume, and altered sodium and chloride excretions. Multiple dose studies also elicited renal toxicity. Following dosing up to 9 days duration at IV doses ≥ 200 mg/kg/day, kidney findings included increased BUN and creatinine, and increased ratios of excreted sodium and chloride compared to creatinine. Mild-to-marked acute tubular necrosis occurred at AUC values of > 1,130,000 ng•hr/mL. Additional nephrotoxicity studies were conducted to evaluate these renal changes and all such studies were consistent in the identification of a no-observed-adverse-effect-level (NOAEL) of 100 mg/kg/day in the rabbit with respect to acute tubular necrosis. Per Dr. Wu and Miele's reviews, renal toxicity was noted only in the rabbit and may have been related to the formation of the acyl glucuronide or other unidentified metabolite, which was not observed in other species or in humans.

- In vitro peramivir did not affect the hERG channel current at the maximum feasible concentration of 300 μM (≈115 ug/ml; ≈AUC=2760 ug.h/ml).

Peramivir is pregnancy category C. There are no adequate and well-controlled trials of peramivir in pregnant women. Because animal reproduction studies are not always

predictive of human response, and peramivir has been shown to cross the placenta in animal studies, peramivir should be used during pregnancy only if clearly needed.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology reviewers were Drs. Leslie Chinn and Jeffry Florian with secondary review provided by Dr. Islam Younis.

Dedicated clinical pharmacology studies were conducted to characterize the pharmacokinetics (PK) of peramivir and were supplemented by sparse plasma concentration data from Phase 2 and 3 clinical trials. The pharmacokinetic parameters following IV administration of peramivir (0.17 to 2 times the recommended dose) showed a linear relationship between dose and exposure parameters (C_{max} and AUC). Dose selection was based on PK/PD simulations. Based on a PD endpoint of time above viral IC_{50} the Review Team determined that the 600 mg dose may provide additional benefit over the 300 mg dose, especially during influenza seasons in which neuraminidase resistance is not prevalent.

Other pertinent PK data include the following and appear in product labeling:

- Peramivir is not a substrate for CYP enzymes, does not inhibit glucuronidation in vitro, and is not a substrate or inhibitor of P-glycoprotein mediated transport.

- Peramivir is not significantly metabolized in humans. The elimination half-life of peramivir following IV administration of 600 mg as a single dose to healthy subjects is approximately 20 hours.

- The major route of elimination of peramivir is via the kidney. Renal clearance of unchanged peramivir accounts for approximately 90% of total clearance and peramivir is primarily cleared by glomerular filtration. Negligible accumulation was observed following multiple doses, either once or twice daily, for up to 10 days.

- In a renal impairment study, 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 clearances of 50-79, 30-49, and 10-29 mL/min, respectively. Further, hemodialysis was effective in reducing systemic exposure of peramivir by 73% to 81%. A reduced dose of peramivir is recommended for patients with creatinine clearance below 50 mL/min as outlined in Section 2.2 *Dosage and Administration* in product labeling based on population PK simulations that indicated that these dose reductions would result in systemic peramivir exposures approximating those observed in patients with normal renal function.

- Based on a population pharmacokinetic analysis including race as a covariate, the volume of distribution was dependent on weight and Asian race, however no dose adjustment is required based on those factors. Regarding gender and age, peramivir pharmacokinetics were similar in male and female subjects and in elderly subjects compared to non-elderly subjects.

- There was no evidence of drug-drug interactions when peramivir was administered with oral oseltamivir or oral contraceptives containing ethinyl estradiol and levonorgestrel; or when peramivir IM was administered with oral probenecid.

6. Clinical Microbiology

Please see extensive reviews by Drs. Takashi Komatsu and Eric Donaldson who conducted the review of virology and resistance data, with supervisory concurrence by Dr. Jules O'Rear. Our virology review staff concluded that peramivir is approvable with respect to virology for the treatment of acute uncomplicated influenza caused by viruses susceptible to peramivir.

The activity of peramivir was assessed in biochemical studies and cell culture assays. As excerpted from the Virology Review, in biochemical studies using neuraminidase inhibition as the endpoint, the median IC_{50} values of peramivir were 0.16 nM (n=44; range (b) (4) nM), (b) (4) nM (n= (b) (4); range (b) (4) nM), 0.13 nM (n=32; range 0.05-11 nM), (b) (4) nM (n= (b) (4) range (b) (4) nM), and (b) (4) nM (n= (b) (4); range (b) (4) nM) against influenza A/H1N1, A/H2N2, A/H3N2, and A/H5N1 viruses, and influenza B virus, respectively. Against 2009 A/H1N1 influenza virus isolates, the IC_{50} values ranged from 0.03-0.5 nM (Gubareva et al., 2010). Of note, the activity of peramivir, like oseltamivir and zanamivir, is less against influenza B virus. The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, inhibition of influenza virus replication *in vivo*, and inhibition or reduction of infection-related symptoms in humans has not been established.

Clinical virology analyses were conducted to evaluate the antiviral efficacy and virological resistance of IV or IM peramivir in subjects with acute uncomplicated influenza virus infection and serious influenza virus infection who were hospitalized. The inclusion criteria for most of the studies described above required a positive rapid antigen test (RAT) for influenza virus. The RAT assays used in these studies are less sensitive against influenza B virus and fewer subjects infected with influenza B virus were enrolled compared to surveillance data. A post-marketing commitment will be recommended because conclusions about efficacy in subjects infected with influenza B virus cannot be drawn.

Influenza A and B virus isolates with amino acid substitutions associated with reduced susceptibility to peramivir were observed in clinical isolates from clinical trials with peramivir and during community surveillance studies; these isolates appear in tabular format in product labeling in section 12.4 in Table 4 below.

Table 4 (from product labeling): Neuraminidase Amino Acid Substitutions Associated with Reduced Susceptibility to Peramivir in Clinical Virus Isolates

Protein		Type / Subtype		
		Influenza A/H1N1 (N1 numbering)	**Influenza A/H3N2**	**Influenza B (B numbering in brackets)**
NA	Clinical Trial	H275Y	R292K, N294S	-
	Community Surveillance Studies	I223R/V, S246N, H275Y	E119V, Q136K D151A/E/G/N/V	P141S (P139S), D198E/N/Y (D197E/N/Y), I222T/V (I221T/V), R371K (R374K)

Cross-resistance to oseltamivir and/or zanamivir was observed for some peramivir resistance pathways. Peramivir shares more resistance pathways with oseltamivir than with zanamivir. Importantly, the HA N63K and N145D substitutions selected in cell culture in the absence of substitutions in NA, conferred cross-resistance to both oseltamivir and zanamivir.

Only the NA H275Y amino acid substitution developed in influenza A/H1N1 virus from more than one subject. All of the isolates with the NA H275Y substitution had reduced susceptibility to peramivir and oseltamivir, but not to zanamivir. For subjects infected with influenza A/H3N2 virus, there were no amino acid substitutions that developed in more than one subject.

7. Clinical/Statistical-Efficacy

The clinical review was conducted by Dr. Peter Miele with secondary review provided by Dr. Linda Lewis who also served as the CDTL. The Biometrics review was conducted by Dr. Tom Hammerstrom with secondary review provided by Dr. Greg Soon and supervisory review provided by Dr. Dionne Price. The set of trials that formed the basis of approval contained in the NDA was agreed upon with the Applicant after discussions beginning shortly after the 2009 influenza pandemic. Efficacy and safety analyses focused on four placebo-controlled trials conducted in adults with acute, uncomplicated influenza (621, 211, 212, and 311). The NDA submission also included data from an active-control trial 631 that compared peramivir to oseltamivir and from studies in high-risk or hospitalized subjects which were included in some of the safety analyses. It is important to note that efficacy results from 212 were not similar to the other three placebo-controlled trials, presumably because it was conducted during the 2008-2009 influenza season when the dominant circulating strain of influenza A/H1N1 virus had the NA H275Y substitution.

Principal study 621 was a three-arm randomized, multicenter, blinded trial conducted in Japan that evaluated a single IV administration of peramivir 300 mg, peramivir 600 mg, or placebo administered over 30 minutes in subjects 18 to 65 years of age with acute uncomplicated influenza. Subjects were eligible if they had fever greater than 38°C (axillary) and a positive rapid antigen test for influenza virus, with at least two symptoms (cough, nasal symptoms, sore throat, myalgia, chills/sweats, malaise, fatigue, or headache) of moderate severity within 48 hours of enrollment. In addition, all subjects enrolled were allowed to take fever-reducing medications The primary endpoint was time to alleviation of symptoms (TTAS), was defined as the number of hours from initiation of study drug until the start of the 24 hour period in which all seven symptoms of influenza (cough, sore throat, nasal congestion, headache, feverishness, myalgia and fatigue) were either absent or present at a level no greater than mild for at least 21.5 hours. This endpoint was similar to the endpoint used for approvals of the other antiviral drugs for acute uncomplicated influenza.

The overall efficacy population (n=297), consisted of subjects with confirmed influenza and administered study drug. Among those enrolled in the peramivir 600 mg dose group (n=98), 55% were male; 34% were smokers; 99% were infected with influenza A virus and 1% were infected with influenza B virus. The results of the trial were robust and showed that subjects receiving peramivir 600 mg experienced alleviation of their combined influenza symptoms a median of 21 hours sooner than those receiving placebo. The median time to recovery to normal temperature in the 600 mg group was approximately 12 hours sooner compared to placebo.

Dr. Hammerstrom conducted a sensitivity analysis that pooled data from all four placebo-controlled trials of acute, uncomplicated influenza that excluded subjects with missing diary card information. Results from the pooled analysis are shown in the following table taken from Dr. Miele's Clinical Review and the corresponding Kaplan-Meier curves that are in the subsequent figure. As stated in Dr. Miele's review, these observations support the primary endpoint findings of Study 621.

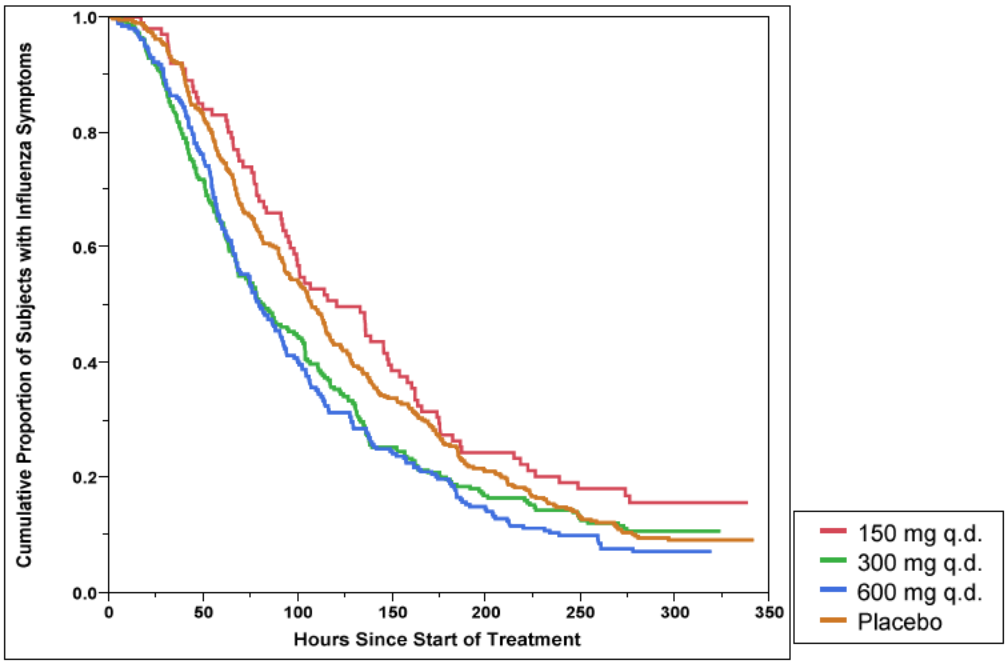
Median Time to Alleviation of Symptoms by Treatment Group in Subjects with Confirmed Influenza - Pooled Placebo-Controlled Trials in Acute Uncomplicated Influenza

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.

Kaplan-Meier Curves for Duration of Influenza Symptoms (ITTI)

Placebo-Controlled Trials in Acute Uncomplicated Influenza (Pooled)



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

Per Dr. Miele's review, the overall median TTAS for peramivir-treated subjects in the pooled analysis was 87.6 hours, which represented a substantial improvement compared with placebo (107.3 hours). Similar trends were noted in the individual trials, with subjects treated with peramivir demonstrating a more rapid TTAS compared with subjects who received placebo. As shown in the figure above, the duration of influenza symptoms was shortest in subjects treated with peramivir 300 mg and 600 mg. Overall, both the Clinical and Statistical reviewers' independent analyses confirmed the Applicant's conclusions of effectiveness based primarily on 621 with support from the placebo-controlled trials as well as an analysis of key secondary endpoints.

8. Safety

Safety information from the overall peramivir development program was reviewed and also included information from clinical trials conducted in hospitalized influenza patients, an open-label Japanese study in pediatric subjects, the postmarketing information regarding the safety of IV peramivir reported from Japan and safety information collected during the 2009 EUA and emergency IND experience.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to

rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following wording appears in product labeling:

Across the five controlled trials in adults with acute uncomplicated influenza, a total of 1,399 subjects were exposed to at least one dose of peramivir. Among the 664 subjects receiving peramivir 600 mg (intravenous or intramuscular), the most commonly observed adverse reaction was diarrhea, occurring at a rate of 8% versus 7% in subjects receiving placebo. No subject receiving peramivir 600 mg experienced a serious adverse event and less than 1% discontinued study because of an adverse reaction.

Clinically significant laboratory abnormalities (DAIDS Grade 2-4) listed in Table 2 in product labeling occurred more frequently in subjects treated with peramivir 600 mg (intravenous or intramuscular) than placebo. Only events occurring at ≥2% are included.

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

Laboratory Parameter Abnormality [a]	PERAMIVIR 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 (≥ 6.0 x ULN)	(N=654) 4%	(N=431) 2%
Neutrophils (< 1.000 x10^9/L)	(N=654) 8%	(N=430) 6%

a. Frequencies based on treatment-emergent laboratory abnormalities

Warnings and Precautions also appear in product labeling for serious skin and hypersensitivity reactions and neuropsychiatric events; wording for neuropsychiatric events is consistent with class labeling for other neuraminidase inhibitors.

Deaths

One death occurred in the six phase 2/3 trials. It was due to meningitis and was deemed unlikely related to study drug.

9. Advisory Committee Meeting

The application was not presented before the Antiviral Drugs Advisory Committee because it was the third drug in the class of neuraminidase inhibitors. Further, a preliminary review of the NDA, including labeling did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion.

10. Pediatrics

Per Dr. Lewis' CDTL memorandum, BioCryst 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.

11. Other Relevant Regulatory Issues

No other substantive regulatory issues have been identified except for a final report on facilities inspections.

Recommended Postmarketing Requirements and Commitments include the following to which the Applicant agreed.

Required Pediatric Assessments under PREA

2831-1 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.

Final Protocol Submission: 11/10/2014
Study/Trial Completion: 04/30/2018
Final Report Submission: 12/31/2018

Postmarketing Requirements under 505(o)

2831-2 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.

Final Protocol Submission: Completed
Study/Trial Completion: Completed
Final Report Submission: 06/30/2015

2831-3 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).

Final Protocol Submission: 04/30/2015
Study/Trial Completion: 04/30/2016
Final Report Submission: 10/31/2016

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

2831-4 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.

Final Protocol Submission: 06/30/2015
Study/Trial Completion: 12/31/2018
Final Report Submission: 06/30/2019

2831-5 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.

Final Protocol Submission: 06/30/2015
Study/Trial Completion: 04/30/2018
Final Report Submission: 12/31/2018

2831-6 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.

Final Protocol Submission: 06/30/2015
Study/Trial Completion: 04/30/2018
Final Report Submission: 12/31/2018

2831-7 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 (b) (4)

Final Protocol Submission: 06/30/2015
Study/Trial Completion: 04/30/2018
Final Report Submission: 12/31/2018

12. Labeling

Final negotiations related to labeling have been completed.

13. Decision/Action/Risk Benefit Assessment

This comprehensive NDA contained multiple clinical trials examining the use of peramivir in the treatment of acute uncomplicated influenza. IV Peramivir was demonstrated to be both efficacious and well-tolerated with a manageable safety profile. Drug-drug interactions are also manageable and product labeling adequately conveys this issue and other safety considerations.

It is important to note that the use of peramivir was not shown to be efficacious in patients with serious influenza requiring hospitalization in a randomized placebo-controlled trial, Study 301. In this trial, 398 subjects were randomized to receive IV peramivir 600 mg daily for 5 days plus standard of care versus standard of care plus placebo within 72 hours of start of symptoms. The primary endpoint was time to clinical 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. Peramivir plus standard of care did not improve median time to clinical resolution compared with standard of care alone. Possible reasons for failure include whether the primary endpoint was appropriate or even whether the dose was correct for this patient population. A description of this clinical trial appears in product labeling to inform the health care provider of the results in a population different than the one for which the treatment is indicated.

In sum, I am in agreement with the conclusions of the multidisciplinary review team that the benefit-risk assessment favors approval of IV peramivir pending satisfactory outcome of manufacturing inspections. This convenient and well-tolerated regimen consisting of one dose of peramivir will address the need for an intravenous antiviral for the treatment of acute uncomplicated influenza, such as use in populations unable to take oral medication, use in patients presenting to emergency rooms and clinics, and general use in patients without the burden of adherence.

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/s/

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12/01/2014