Clinical and Cross-Discipline Team Leader Review

Date	January 20, 2021
From	Peter Miele, MD
Subject	Clinical and Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 206426/S-007
Applicant	BioCryst Pharmaceuticals, Inc.
Date of Submission	July 29, 2020
PDUFA Goal Date	January 29, 2021
Proprietary Name	Rapviab®
Established or Proper Name	Peramivir
Dosage Form(s)	200 mg in 20 mL (10 mg/mL) single use vials
Applicant Proposed Indication(s)/Population(s)	Treatment of acute uncomplicated influenza in patients 6 months and older who have been symptomatic for no more than two days
Applicant Proposed Dosing Regimen(s)	Adults and adolescents (13 years and older): 600 mg single dose Pediatric patients (6 months to 12 years): 12 mg/kg (up to 600 mg) single dose
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed by Applicant
Recommended Dosing Regimen(s) (if applicable)	Same as proposed by Applicant

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Children younger than 5 years old, and especially those younger than 2 years, are at increased risk of serious influenza and its related complications, which can result in hospitalization and death. The U.S. Centers for Disease Control and Prevention (CDC) recommends prompt initiation of antiviral drugs in young children with suspected or confirmed influenza of any severity. Currently, the only antiviral drug approved in the U.S. for use in children younger than 2 years is oseltamivir (Tamiflu®), an oral neuraminidase inhibitor (NAI) prodrug that is administered twice daily for 5 days and widely used for the treatment of influenza. Despite the availability of oseltamivir, there exists a need for an effective anti-influenza treatment option for infants who may present to an urgent care or emergency department setting and for whom oral dosing with oseltamivir may not be feasible.

Rapivab® (peramivir) for injection, another drug in the NAI class, is currently approved in the U.S. for treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days. The recommended dosage in pediatric patients is a single 12 mg/kg dose (maximum 600 mg) given by intravenous (IV) infusion over 15-30 minutes. The pediatric approval of Rapivab (in 2017) was based on clinical data from Study BCX1812-305 (Study 305), a Phase 3 open-label trial in pediatric patients with acute uncomplicated influenza randomized to treatment with IV peramivir 12 mg/kg or oral oseltamivir within 48 hours of symptom onset. In this supplemental application, BioCryst Pharmaceuticals, Inc. (Applicant) has submitted new data from Study 305 from a cohort of subjects 6 months to 2 years old to support expansion of the Rapivab indication to this pediatric subgroup.

Clinical data in 18 subjects treated with IV peramivir in this youngest cohort support a favorable safety profile of the drug in children 6 months to 2 years old. There were no deaths or serious adverse events (AEs) in Study 305 overall. Three subjects in the youngest cohort had 4 AEs (runny nose, gastroenteritis, diarrhea and vomiting), all of which were mild and none of which were considered related to peramivir or resulted in drug discontinuation. Laboratory toxicities were few and mostly mild or not clinically significant. Two subjects in the cohort developed low neutrophil counts following IV peramivir administration. The cause of these laboratory findings is not clear, and may have been related to influenza infection, but they were not considered clinically significant by the investigators. Treatment-emergent low neutrophil count was also observed in the older age cohorts of Study 305, as well as in the adult clinical trials of peramivir, and is currently listed in Rapivab labeling as an adverse reaction. In sum, the safety of IV peramivir in infants younger than 2 years was consistent with that seen in older children and adults treated with peramivir. No new safety concerns were identified and no infusion-related toxicities were described in this age group.

Study 305 was not powered to formally compare the effectiveness of IV peramivir versus oral oseltamivir in pediatric subjects. Nonetheless, clinical outcomes such as the time to alleviation of influenza symptoms or the time to resolution of fever in subjects 6 months to 2 years old were comparable to those seen in older children treated with IV peramivir or in children treated with oral oseltamivir. In addition, no major differences were noted between age

cohorts or treatment groups with respect to the usage of fever-reducing medicines, return to normal activities, return to normal eating patterns, or decreases in influenza viral shedding over time. There were no cases of influenza-related complications in this age cohort, nor was there evidence of emergent drug resistance in the trial overall.

Peramivir blood levels in children younger than 2 years old were noted to be about 30% lower than in healthy adults without flu; however, the levels in these young children were within the range of drug concentrations observed in a separate trial of elderly adults with acute uncomplicated influenza who were treated with IV peramivir 600 mg and resolved their illness. Given this, the FDA concluded that the lower drug concentrations in infants younger than 2 years were not likely to be clinically significant. The trends in clinical outcomes described above would seem to bear this out.

In conclusion, clinical data from Study 305 showed that treatment with IV peramivir in children 6 months to 2 years old with acute uncomplicated influenza was safe and well tolerated. In addition, peramivir demonstrated activity in this age group comparable to that seen in older children treated with IV peramivir or in children treated with oral oseltamivir, as measured by both virologic and clinical outcomes. These data support a favorable benefit-risk assessment for IV peramivir in this age group and extension of the Rapivab indication as proposed by the Applicant.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza (flu) is a seasonal viral infection that affects 5% to 20% of the U.S. population each year, according to the U.S. Centers for Disease Control and Prevention (CDC). • Influenza typically results in an acute uncomplicated illness with fever and respiratory symptoms that self-resolve within 3 to 7 days. In children, influenza can also present with gastrointestinal (GI) symptoms, such as vomiting and diarrhea. • Each year, millions of children in the U.S. get sick with seasonal flu. Children commonly need medical care because of flu, especially children younger than 5 years old. • Although most cases are self-limiting, influenza can also result in serious illness with complications that can lead to hospitalization or death. • Children younger than 5 years old, and especially those younger than 2 years, are at greater risk of developing serious influenza and related	Influenza infection can be dangerous in young children. Therefore, early treatment with antiviral drugs is recommended in children younger than 5 years old, and especially in children younger than 2 years, as these groups are at greater risk of serious influenza illness and related complications. Early initiation of antiviral drugs is associated with shortened duration of influenza illness and may reduce the incidence of some complications in young children.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	complications. • Early treatment with antiviral drugs has been demonstrated to shorten the duration of influenza symptoms and may reduce the risk of influenza-related complications, such as ear infections in young children. • The CDC and American Academy of Pediatrics (AAP) recommend prompt initiation of antiviral drugs to treat confirmed or suspected influenza of any severity in children at high risk of serious influenza illness, including those younger than 5 years old, and especially those younger than 2 years.	
Current Treatment Options	• There are currently four antiviral drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute uncomplicated influenza and that are recommended for use in children: oseltamivir phosphate (Tamiflu®), zanamivir (Relenza®), peramivir (Rapivab®) and baloxavir marboxil (Xofluza®). Each is approved for treatment of patients who have been symptomatic for no more than 2 days. • Only oseltamivir and peramivir are approved for use in children younger than 5 years old: oseltamivir is approved in patients 2 weeks and older, and peramivir in patients 2 years and older. • Oseltamivir is available as capsules or liquid suspension and is given by mouth, twice a day, for 5 days. • Peramivir is available as an injection formulation that is given as a one-time intravenous (IV) infusion.	Only oseltamivir is currently approved for the treatment of influenza in children younger than 2 years old, who are at greater risk of developing serious illness and complications. Administering medicines to sick infants by mouth, however, can be challenging, especially in cases where an infant cannot tolerate oral medicines, either because of poor compliance with oral medicines in the past or because of acute GI symptoms (not uncommon in young children with flu), or where compliance with a 5-day course is a concern. Thus, there exists a need for alternative treatment options in this age group that are effective and possibly more convenient than oral oseltamivir. Peramivir may provide another option for treatment of influenza in children younger than 2 years old. It is given as a one-time dose by IV, which may of benefit to children seen in urgent care centers or emergency departments, and avoids the problems typically associated with giving medicines by mouth to small children.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The current application provides data from Study BCX1812-305, a Phase 3 open-label trial in pediatric subjects with acute uncomplicated influenza randomized 4:1 to IV peramivir 12 mg/kg or oral oseltamivir. Specifically, data from a cohort of 18 subjects aged 6 months to 2 years treated with IV peramivir within 48 hours of developing symptoms were submitted to support the approval of the drug in this age group. • The above trial was not designed to formally compare the effectiveness of IV peramivir to oral oseltamivir; however, in the cohort of subjects 6 months to 2 years old, IV peramivir demonstrated activity comparable to that seen in older children treated with IV peramivir and those treated with oral oseltamivir, as measured by both clinical and virologic endpoints. • The median time to alleviation of influenza symptoms in this youngest age cohort (n=11) was 76 hours, compared to 79 hours in children 2 to 17 years old treated with IV peramivir (n=70) and 100 hours in children 1 to 17 years old treated with oral oseltamivir (n=16). • The median time to resolution of fever was 35 hours in both the youngest peramivir cohort and the group treated with oseltamivir; it was 40 hours in older children treated with IV peramivir. • There were no cases of influenza-related complications (otitis media, sinusitis, bronchitis, and pneumonia requiring antibiotic use) in the youngest age cohort of the peramivir group. • There were no differences between age cohorts or treatment groups with respect to usage of fever-reducing medicines, return to normal activities, return to normal appetite/eating patterns, or viral shedding over time. • There were no cases of viral resistance to peramivir, or related drugs oseltamivir and zanamivir, in influenza isolates collected during the trial. • Pharmacokinetics analyses showed that peramivir blood levels in the youngest age cohort were about 30% lower than in healthy adults without flu given 600 mg IV peramivir. However, these pediatric drug concentrations were within the range associated with effectiveness in a separate trial of IV peramivir in elderly subjects with acute uncomplicated influenza.	The trends in clinical and virologic outcomes in Study BCX1812-305 indicate that treatment with IV peramivir 12 mg/kg is similarly effective in children 6 months to 2 years old with acute uncomplicated influenza as in older children treated with IV peramivir and comparable to treatment with oral oseltamivir. Although peramivir blood levels in the youngest age group were shown to be lower than in healthy adults, the values were within the range of blood levels seen in a separate trial of elderly subjects with acute uncomplicated influenza who were treated with IV peramivir and resolved their illness. Thus, the lower drug concentrations in children younger than 2 years old are not considered clinically significant. Peramivir's favorable safety profile combined with clinical and virologic outcomes that are in line with other approved anti-influenza drugs indicate a positive benefit-risk assessment in children 6 months to 2 years with uncomplicated influenza and support extension of the Rapivab indication to this age group. The main drawback to treatment with peramivir is the need to insert an IV line. The benefits of IV peramivir (i.e., safety, effectiveness, and single-dose) ought to be weighed against the risk of placing an IV in a sick infant and should be made on case-by-case basis taking into account the patient's condition and wishes of the parent/caregiver.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety profile of IV peramivir in the cohort of subjects 6 months to 2 years (n=18) was favorable. No new safety concerns were identified. • Three subjects had 4 adverse events reported (runny nose, gastroenteritis, diarrhea and vomiting), all of which were mild and none of which were considered related to peramivir or resulted in drug discontinuation. • No infusion reactions were reported in this youngest age cohort. • Laboratory toxicities were few and mostly mild or not clinically significant. Two subjects in this cohort developed low neutrophil counts following IV peramivir administration. The cause of these laboratory findings is not clear, and may have been related to influenza, but they were not considered clinically significant by the investigators. Low neutrophil count was also seen in the older age cohorts of Study 305, as well as in the adult clinical trials of peramivir, and is currently listed in Rapivab labeling as an adverse reaction.	This review did not identify any risks with IV peramivir given under the recommended conditions of use that cannot be adequately managed through product labeling. A new table has been added to Section 2.3 of Rapivab labeling (Preparation of RAPIVAB for Intravenous Infusion) which lists the recommended maximum infusion volumes by age and weight to ensure that volumes administered to young children are within the endotoxin limits set by the U.S. Pharmacopeia (USP).

2. Background

Introduction

According to the U.S. Centers for Disease Control (CDC), 5% to 20% of the U.S. population is infected with influenza each year. Acute uncomplicated influenza is a self-limited febrile illness with respiratory symptoms that usually last from 3 to 7 days. However, influenza also can present as severe illness with related complications that may result in hospitalization and death. Such complications can include dehydration, viral pneumonitis, myocarditis, and rarely, central nervous system involvement. Influenza infection also places patients at increased risk of secondary bacterial infections, such as sepsis, pneumonia, sinusitis, and otitis media. Certain populations are at greater risk for severe influenza and related complications, including the elderly, pregnant women, persons with predisposing conditions, such as asthma, heart disease, and diabetes mellitus, and children younger than 5 years old, in particular those younger than 2 years.

Each year, millions of children in the U.S. become ill with seasonal influenza. The CDC estimates that since 2010, influenza-related hospitalizations among children younger than 5 years old ranged from 7,000 to 26,000 in the United States. Many more have to visit a healthcare provider, urgent care center, or emergency department because of influenza.[1] While relatively rare, some children die from influenza each year. Since 2004-2005, influenza-related deaths in children reported to the CDC during regular influenza seasons have ranged from 37 to 188 deaths; however, it is likely that not all deaths are captured and that the number of actual deaths is higher. (During the 2009 H1N1 pandemic, 358 pediatric flu-related deaths were reported to the CDC from April 2009 to September 2010.)[2]

Therapeutic Context

Clinical trials and observational data show that early antiviral treatment can shorten the duration of fever and influenza symptoms and may reduce the risk of some influenza-related complications (e.g., otitis media in children 1 to 5 years old).[3] Antiviral drugs work best if started within two days of onset of symptoms. The CDC and American Academy of Pediatrics (AAP) recommend prompt initiation of antiviral drugs to treat confirmed or suspected influenza, of any severity, in children at high risk of serious influenza illness, including those younger than 5 years old, and especially those younger than 2 years.

Currently, there are four antiviral drugs approved by the U.S. Food and Drug Administration (FDA) that are recommended for use in pediatric patients: oseltamivir(Tamiflu®), zanamivir (Relenza®), peramivir (Rapivab®), and baloxavir marboxil (Xofluza®), as summarized in Table 1. All of these drugs are indicated for treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 2 days. (Note: the adamantane drugs are no longer recommended for

[1] https://www.cdc.gov/flu/highrisk/infantcare.htm
[2] https://www.cdc.gov/flu/highrisk/children.htm
[3] Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD002744. DOI: 10.1002/14651858.CD002744.pub4.

treatment of influenza due to widespread adamantane resistance among circulating influenza A strains and lack of activity against influenza B).

Table 1: FDA-Approved Recommended Drugs for Treatment of Influenza in Pediatrics

Drug Class	Generic Name	Trade Name	Approved Age Group
Neuraminidase Inhibitor	Oseltamivir phosphate	Tamiflu®	≥ 2 weeks
	Zanamivir	Relenza®	≥ 7 years[a]
	Peramivir	Rapivab®	≥ 2 years
Polymerase Acidic Endonuclease Inhibitor	Baloxavir marboxil	Xofluza®	≥ 12 years

[a] Zanamivir is not recommended for use in patients with underlying airway disease (i.e., asthma and other chronic lung diseases) due to risk of serious bronchospasm and not proven effective in this subset.

Oseltamivir, zanamivir, and peramivir are related anti-influenza drugs in the neuraminidase inhibitor (NAI) drug class. These drugs provide antiviral activity by inhibiting the influenza virus neuraminidase enzyme necessary for releasing viral particles from infected cells. Each of the NAI drugs is approved for use in pediatric patients, with varying age limits (see Table 1). Oseltamivir is available as capsules or liquid suspension for oral administration and zanamivir is available as powder for oral inhalation; the recommended dosage for both is twice daily (BID) for 5 days. Peramivir is available as an injection and is recommended for single-dose intravenous (IV) administration. In contrast, baloxavir is an influenza virus polymerase acidic endonuclease inhibitor (first in class) indicated for use in healthy and high-risk patients 12 years and older. Baloxavir is available as a tablet or liquid suspension for oral administration and is also recommended for single-dose use.

Because children bear a large burden of infection during seasonal influenza and are at greater risk of developing complications, new treatments for children are needed. In particular, there is a significant unmet need for influenza therapies in children <2 years of age,. The only anti-influenza drug currently approved in this age group is oseltamivir. While oseltamivir represents a viable treatment option, it must be administered orally, twice daily, and for 5 days, all of which can pose challenges in sick infants who either may be unable to tolerate an oral product, because of a history of poor compliance with oral medications or because of acute gastrointestinal symptoms (e.g., vomiting and diarrhea), which are not uncommon with influenza in this age group, or in whom compliance with a 5-day treatment regimen is a concern. Thus, there exists a need for additional effective anti-influenza treatment options in patients <2 years old who may present to an urgent care or emergency department setting. As a parenterally administered drug, single-dose IV peramivir may offer an alternative and potentially more convenient treatment option for this age group that circumvents the limitations associated with oral dosing in young children.

Regulatory Background

Rapivab® (peramivir) was approved in the United States in December 2014 (NDA 206426) as a single 600-mg IV dose for the treatment of acute uncomplicated influenza in adults 18 years and older who have been symptomatic for no more than two days. Under the Pediatric Research Equity Act (PREA), the following postmarketing requirement (PMR) was issued in the approval letter, to be fulfilled by December 31, 2018:

PMR 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.

FDA guidance on the development of anti-influenza drugs recommends sponsors conduct adequate and well-controlled trials to fulfill PREA requirements and extend treatment indications to pediatric age groups.[4] Placebo-controlled trials, however, are no longer feasible because of established guidelines to treat most children with confirmed or suspected influenza. The pediatric study plan for Rapivab was discussed with the FDA Pediatric Review Committee (PeRC) in August 2014. The PeRC acknowledged that placebo-controlled pediatric trials were no longer feasible and that superiority trial designs would require prohibitively large sample sizes. Moreover, the short duration (1-2 days) of the treatment effect seen with other anti-influenza drugs precluded the ability to establish a meaningful non-inferiority margin for active-controlled trials. For these reasons, the PeRC and the Division of Antivirals (DAV) agreed that partial extrapolation of effectiveness from adult clinical trials, with bridging pharmacokinetics (PK) and safety data in pediatric subjects, would be an acceptable pathway moving forward. An open-label, active-controlled trial to evaluate PK, safety, and effectiveness of IV peramivir in comparison to oral oseltamivir was considered reasonable. Oseltamivir was selected for the control as it is widely used for treatment of influenza and approved in the U.S. for use in children ≥ 2 weeks of age. While such a trial would not be powered to formally test effectiveness, trends in clinical outcome measurements could be compared with oseltamivir, as well as to the adult clinical trials of peramivir. Such a study design would also have the benefit of providing direct comparative safety data in the pediatric populations of interest.

Accordingly, the Pediatric Study Plan (PSP) for Rapivab submitted with the original NDA consisted of a single clinical trial to fulfill PMR 2831-1. The negotiated protocol (BCX1812-305) featured an open-label, active-control design in which subjects with acute uncomplicated influenza would be randomized 2:1 to receive IV peramivir or oral oseltamivir. The 2:1 randomization was selected to maintain the sample size feasible. The protocol would initially be limited to subjects ≥2 years old but would be expanded to enroll younger age cohorts once safety data in the older cohorts had been reviewed.

Study BCX1812-305 (Study 305), entitled "*A Phase 3, Randomized, Open Label, Active-Controlled Study to Evaluate the Safety, Pharmacokinetics and Effectiveness of IV Peramivir Compared to Oral Oseltamivir in Pediatric Subjects with Acute Uncomplicated Influenza*", was initiated in 2015. Clinical data in subjects 2-17 years old from this trial were submitted to NDA 206426 in March 2017 as an efficacy supplement (S-004) to partially fulfill PMR 2831-1 and support an expanded indication in that age group. The supplemental NDA (sNDA) was approved in September 2017, at which time the FDA noted that the pediatric requirement for ages 2 to <18 years was fulfilled.

The protocol for Study 305 was subsequently amended twice to allow for enrollment of pediatric subjects from ≥28 days to <2 years and from birth to <28 days. However, recruitment difficulties

[4] FDA Guidance for industry *Influenza: Developing Drugs for Treatment and/or Prophylaxis* (April 2011). Available at: https://www.fda.gov/media/73339/download

precluded full enrollment of these age cohorts. In particular, the Applicant reported that a large proportion of patients in this age group were either too ill (requiring hospitalization or intensive care) or suspected of having a bacterial infection/sepsis and thus were ineligible to participate in a trial of uncomplicated influenza. In contrast, parents/caregivers of infants with milder influenza illness were largely unwilling to consent to an IV route of administration given the availability of a licensed, age-appropriate oral product (oseltamivir) for the same indication. Given these challenges, in December 2018, the FDA agreed to extend the final report submission date for PMR 2831-1 to March 31, 2021, and advised the Applicant to enhance its recruitment efforts.

Following enhanced recruitment activities in 2018-2019, including opening two new sites in South Africa, enrollment in the ≥28 days to <2 years cohort was completed by late 2019 (age range 5.6 to 23.2 months). Study 305, however, failed to enroll any subjects in the birth to <28 days cohort and was subsequently closed due to futility in enrolling infants younger than 6 months of age.

The current sNDA (S-007) was submitted on July 29, 2020 to support inclusion of pediatric patients ≥6 months in the approved Rapivab indication. Clinical PK, safety, and effectiveness data with IV peramivir in the ≥28 days to <2 years old cohort of Study 305 were submitted to support an expanded indication; however, because the trial failed to enroll subjects <6 months old, with only one such subject (5.6 months old) enrolled, the sNDA seeks approval down to 6 months rather than 28 days of age.

3. Product Quality

Rapivab (peramivir) injection for IV use is formulated as 10 mg/mL drug substance in 0.9% sodium chloride, marketed as 200 mg per 20 mL single-use vials. The formulation used in the pediatric Study 305 is the marketed formulation. The composition has not changed since the original application and no new chemistry or manufacturing information was submitted with this sNDA.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies were previously conducted for peramivir and reviewed in prior submissions; no new studies were submitted in the current sNDA.

5. Clinical Pharmacology

The dose of IV peramivir evaluated in Study 305 in subjects ≥6 months old was 12 mg/kg, administered as a single infusion over a minimum of 15 minutes. This dose was selected based on simulation results from a population PK model developed using data from nine peramivir studies. Peramivir exposure in healthy adults who received a 600 mg IV dose in Study BCX1812-113 (Study 113), a Phase 1 PK study that compared IV and intramuscular (IM) peramivir, provided the target peramivir exposure for these model simulations.

The analysis of PK at the 12 mg/kg dose was a secondary endpoint of Study 305 and was conducted only in peramivir-treated subjects with sufficient blood samples. PK blood samples were collected at four time-points: immediately following completion of infusion, 30 minutes to 1 hour post-

infusion, 1-3 hours post-infusion, and 3-6 hours post-infusion. The following PK parameters were evaluated: C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}3h}$, T_{max}, and T_{last}.

Of the 20 peramivir-treated subjects in the ≥28 days to <2 years cohort of Study 305, C_{max} was reported for 18 subjects and $AUC_{0\text{-}3h}$ for 15 subjects. A remote record review of the trial's bioanalytical site ((b) (4)) conducted by the FDA Office of Study Integrity and Surveillance (OSIS) reported no issues that would impact the reliability of these PK data (onsite inspections were not possible due to the ongoing COVID-19 pandemic).

Interim PK results from Study 305 had previously shown that peramivir exposure in pediatric subjects ≥2 years old administered a 12 mg/kg or 600 mg IV dose was not markedly different compared with healthy adults who received a 600 mg IV dose (Study 113). In this submission, however, peramivir C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}3h}$ values in subjects <2 years old were found to be lower than the geometric mean (GM) values observed in healthy adults or in the older cohorts of Study 305 (median T_{max} and T_{last} were similar across all cohorts). The FDA Clinical Pharmacology reviewers found no relationship between age or weight and peramivir exposure in the youngest age cohort to account for this lower exposure, nor was an exposure-response relationship identified based on a time to alleviation of symptoms (TTAS) endpoint (refer to the Clinical Pharmacology review by Dr. Mario Sampson for further details).

The geometric mean ratio (GMR) and 90% confidence intervals (CI) for subjects ≥6 months to <2 years old versus healthy adults (Study 113) was 0.68 (0.52, 0.88) and 0.83 (0.59, 1.18) for $AUC_{0\text{-}3h}$ and C_{max}, respectively. To put this ~30% lower AUC into context, the FDA Clinical Pharmacology reviewers compared peramivir exposure in this youngest cohort with that associated with effectiveness in Study BCX1812-306 (Study 306), a Phase 3 trial of IV peramivir 600 mg in elderly subjects with acute uncomplicated influenza. Peramivir $AUC_{0\text{-}1hr}$ was used for this comparison because of differences.in PK sampling. In Study 306, peramivir $AUC_{0\text{-}1hr}$ following a 600 mg IV dose was not associated with TTAS, nor was it found to be significantly different compared with healthy adults in Study 113 ($AUC_{0\text{-}1h}$ GMR [90% CI]: 0.94 [0.75, 1.18]. Importantly, all subjects from the youngest cohort of Study 305 had $AUC_{0\text{-}1hr}$ values above the minimum $AUC_{0\text{-}1hr}$ value reported in Study 306 (two subjects in Study 305 had $AUC_{0\text{-}1hr}$ values below the 5th percentile of $AUC_{0\text{-}1hr}$ values in Study 306). Based on these observations, the FDA Clinical Pharmacology reviewers concluded that the ~30% lower AUC in subjects <2 years old compared with healthy adults was not likely to be clinically significant.

6. Clinical Microbiology

In Study 305, bilateral mid-nasal swab specimens were collected for virologic analysis from all enrolled subjects at baseline (pre-dose) and on Days 3, 7, and where possible on Day 14. Virology laboratory tests included viral subtype characterization from the baseline sample, laboratory culture and analysis by log_{10} tissue culture infective dose 50% ($TCID_{50}$), and reverse transcriptase polymerase chain reaction (RT-PCR) assay. Specimens from all subjects yielding influenza virus were assessed for susceptibility to NAIs (Day 1 and last specimen yielding influenza virus on culture). A central laboratory performed all virologic assessments. Changes in viral shedding, by log_{10} $TCID_{50}$/mL titer and RT-PCR, and in viral susceptibility to NAIs were secondary endpoints.

Tthe Intent-to-Treat Infected (ITTI) population in the ≥ 28 days to <2 years old cohort of Study 305 consisted of 12 subjects, all of which had positive influenza results by RT-PCR at baseline, and 9 of which had positive baseline titers by log_{10} $TCID_{50}$/mL (peramivir 8, oseltamivir 1). By Day 7, only 1 subject (in the peramivir group) had detectable virus titer by log10 TCID50/mL, and by Day 14, none did. By Day 14, the proportion of subjects with positive RT-PCR results dropped to 5/11 (45%) and 0/1 (0%) in the peramivir and oseltamivir groups, respectively. These results were not notably different compared with the older cohorts of Study 305. There were no significant changes in virus susceptibility to NAIs among the virus isolates recovered in the ≥ 28 days to <2 years cohort. For Study 305 overall, no treatment-emergent genotypic changes previously associated with reduced susceptibility to peramivir (including the H275Y substitution) were identified in any subject treated with peramivir or oseltamivir.

As part of this submission, Section 12.4 of Rapivab labeling will be updated to include additional resistance-associated substitutions based on sponsor-generated data and published studies, including evaluations of peramivir resistance in zoonotic influenza strains (e.g. A/H5N1 and A/H7N9), as requested by FDA. Refer to the Virology Review by Dr. William Ince for details.

7. Clinical - Efficacy

As previously stated, this pediatric sNDA submission includes safety, effectiveness, and PK data from subjects in the ≥28 days to <2 years old cohort of the pivotal trial Study 305. Difficulties in recruiting the youngest age cohorts precluded enrollment of subjects <6 months old, with only one such subject (5.6 months old) enrolled; thus, the sNDA seeks approval down to age 6 months rather than 28 days. Study 305, however, was not powered for efficacy comparisons. Instead, the pediatric approval of IV peramivir in patients ≥6 months to <2 years old will be based on extrapolation of efficacy from the adult trials, bridging PK and demonstration of safety in this age group. Clinical outcomes with IV peramivir in the youngest age cohort will be compared to the older cohorts of Study 305, as well as to the oseltamivir arm, but these comparisons are supportive only.

Study Design

Study 305 was a Phase 3, multi-center, open-label, randomized, active-controlled trial initially conducted in pediatric subjects ≥2 years of age in the United States. The original protocol, dated November 5, 2014, was amended five times as summarized below (the information submitted in this supplement is based on Protocol Amendment 5, Version 6.0):

- Protocol Amendment 2, Version 3.0 (dated June 21, 2015):
  - The lower age limit was changed from 2 years to 28 days
  - The IV peramivir to oral oseltamivir randomization ratios were changed from 2:1 to 4:1 for each age cohort
- Protocol Amendment 3, Version 4.0 (dated October 20, 2016):
  - The lower age limit was changed from 28 days to birth
  - The remaining subjects <7 years old to be enrolled in the trial would all be assigned to IV peramivir
- Protocol Amendment 4, Version 5.0 (dated January 10, 2017):
  - The dose of IV peramivir in subjects <6 months of age was changed from 12 to 8 mg/kg

- A new peramivir dilution protocol for children <12 months of age was put into effect, as shown in Table 2.

Table 2: Peramivir Dilution for Pediatric Patients <12 Months of Age (Study 305)

Age		Dosing			
		Anticipated Approximate Volume of Undiluted Drug Product	Volume of Diluted Drug Product Infused	Total mEq of Na Infused	Number of Vials Per Dose
0 - < 28 days (3 kg to 5.5 kg)	Dilute dose to 12 mL total	2.4 to 4.4 mL	12 mL	1.5 to 1.2	1
28 days to < 3 months (3 kg to 7.5 kg)	Dilute dose to 20 mL total	2.4 to 6.0 mL	20 mL	2.7 to 2.2	1
3 months to < 6 months (4.5 kg to 11.2 kg)	Dilute dose to 25 mL total	3.6 to 4.7 mL	25 mL	3.3 to 3.1	1
6 months to < 12 months (4.5 kg to 11.2 kg)	Dilute dose to 25 mL total	7.2 to 13.4 mL	25 mL	2.7 to 1.8	1

Source: Protocol BCX1812-305, Version 5.0 (dated January 10, 2017)

- Protocol Amendment 5, Version 6.0 (dated November 5, 2018) - *these changes made to facilitate enrollment of subjects <2 years old*:
  - Inclusion criteria were changed from onset of influenza symptoms no more than 48 hours before screening to onset no more than 72 hours before screening for subjects <2 years old
  - Exclusion criteria were modified to allow enrollment of subjects with identified risk factors, including subjects with immunocompromised status (but not severe immunocompromise)

In addition, the Applicant opened two new sites in South Africa during the 2019 Southern Hemisphere influenza season to increase enrollment of subjects <2 years of age.

The primary objective of Study 305 was to evaluate the safety of IV peramivir compared with oral oseltamivir in pediatric subjects with acute uncomplicated influenza. Key secondary objectives were to (1) describe the PK of IV peramivir in pediatric subjects with influenza, (2) evaluate the effectiveness of IV peramivir compared with oral oseltamivir in pediatric subjects with influenza, and (3) evaluate the incidence of influenza complications, specifically otitis media, sinusitis, bronchitis, or pneumonia requiring antibiotic use diagnosed after initiation of study drug. This section will focus on the protocol elements as they pertained to subjects <2 years of age (for discussion of study design in the older age cohorts, refer to the clinical review of NDA 206426/S-004, dated August 24, 2017).

Key inclusion criteria for subjects <2 years old (based on Protocol Amendment 5) were onset of symptoms ≤72 hours before presentation for screening, and either a positive influenza rapid antigen

test (RAT) or clinical signs and symptoms consistent with acute influenza infection. Subjects presenting with fever (oral temperature ≥100°F [37.8°C] or rectal temperature ≥101.3°F [≥38.5°C]) and at least one respiratory symptom (cough or rhinitis) when influenza virus was known to be circulating in the community were considered to have clinical symptoms consistent with acute influenza. Fever had to be documented at the time of screening or reported by the parent/caregiver if the subject received an antipyretic medication within 6 hours prior to the screening assessment.

- Note: enrollment at each site by clinical symptoms alone was approved by the sponsor at the beginning of each influenza season once influenza was confirmed in the local community. The sponsor could withdraw approval for symptomatic screening in any season based on trends in influenza surveillance data. Prior to sponsor approval or after approval was withdrawn, a positive influenza RAT was needed for inclusion.

Key exclusion criteria for subjects <2 years old included history of premature birth (<36 weeks gestation), weight <3.0 kg, onset of symptoms >72 hours before presentation for screening, complicated influenza (i.e., intensive care, evidence of organ dysfunction, proven/suspected concomitant bacterial infection, or other concomitant viral infection, like respiratory syncytial virus bronchiolitis), or presence of severe immunocompromised status (due to chronic disease or illness, previous organ transplant, or use of immunosuppressive therapy which would include oral or systemic treatment with >10 mg prednisone or equivalent on a daily basis within 30 days of screening). Subjects were also excluded if they developed symptoms while hospitalized for another indication or received a live attenuated influenza vaccine within 14 days of presentation.

Subjects were enrolled according to the following age-based cohorts: birth to <28 days (up to 10 subjects) and 28 days to <2 years old (up to 20 subjects). Enrolled subjects were randomized at a 4:1 ratio to receive either a single dose of IV peramivir or 5 days of twice daily (BID) dosing of oral oseltamivir. No blinding was performed, and sample sizes were not based on statistical considerations for detecting statistical differences.

The doses of IV peramivir planned for evaluation were 12 mg/kg for subjects ≥6 months and 8 mg/kg for subjects <6 months; however, no subjects <6 months old were enrolled. These doses were based on population PK modeling performed by the FDA (July 2010) and sponsor modeling of peramivir exposure based on Studies 0918T0633 (children and adolescents) and 0722T0621 (adults), in addition to other studies, that supported these target doses in order to achieve exposure similar to that in adults receiving 600 mg IV peramivir (Study 113). Oseltamivir dosing was weight-based (30 mg BID for ≤15 kg, 45 mg BID for 15.1 - 23 kg, 60 mg BID for 23.1 - 40 kg, and 75 mg BID for >40 kg).

After initiating treatment on Day 1, subjects underwent follow-up assessments on Day 3 (home or clinic visit), Day 7 (clinic visit) and Day 14 (home visit, clinic visit, or if neither possible a follow-up phone call). Parents/caregivers were instructed to record the following assessments daily in a Subject Diary: body temperature, age-specific clinical symptoms of influenza, usage of antipyretic medications, ability to perform usual daily activities, and appetite/eating patterns. Table 3 summarizes the Subject Diary assessments and recording frequencies. Body temperature measurements were recorded until temperature normalized for 48 hours without the usage of antipyretic medication. Assessments of age-specific signs and symptoms of influenza were recorded

until symptom resolution and through the last follow-up visit (whichever came first). Assessments for antipyretic usage (acetaminophen or ibuprofen), ability to perform usual activities, and appetite/eating patterns were recorded through the final follow-up assessment.

Table 3: Subject Diary Assessments (Study 305)

Assessment	Recording Frequency
Body Temperature (oral or axillary)[a]	Twice daily
Usage of antipyretic medication (acetaminophen or ibuprofen)	Whenever applicable
Age-specific signs and symptoms of influenza ≤ 3 years: five influenza symptoms[b] ≥ 4 to < 7 years: 7 influenza symptoms[c] ≥ 7 years: 7 influenza symptoms[d]	Twice daily on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe)
Ability to perform usual daily activities (i.e., return to day care/school or resume pre-illness activity)	Once daily on a 0-10 visual analogue scale (lower score = lower activity ability)
Appetite and eating patterns	Once daily as normal or reduced/abnormal

[a] To avoid confounding effects of antipyretic medications, temperature measurements were to be taken, whenever possible, immediately before or at least 4 hours after administration of antipyretic medications.
[b] Subjects 28 days to <4 years old had the following 5 influenza symptoms assessed: cough, rhinitis, feverishness, malaise/irritability, and gastrointestinal symptoms (nausea, vomiting, or diarrhea).
[c] Subjects ≥ 4 to <7 years old had the following 7 influenza symptoms assessed: cough, sore throat, nasal obstruction, myalgia (muscle aches), headache, feverishness, and GI symptoms (nausea, vomiting, or diarrhea)
[d] Subjects ≥ 7 years old had the following 7 influenza symptoms assessed: cough, sore throat, nasal obstruction, myalgia (muscle aches), headache, feverishness, and fatigue
Source: Adapted from Table 7.1-1 of Clinical Review of NDA 206426/S-004 by Dr. Mark Needles

Following IV peramivir administration, subjects had four 1.0 mL PK samples collected at the following time points: immediately following completion of infusion, 30 minutes to 1 hour post-infusion, 1-3 hours post-infusion, and 3-6 hours post-infusion. (Note: subjects weighing <5 kg were to have only two 1.0 mL blood samples: one time immediately following completion of infusion and one time between 1-3 hours post-infusion.) The analysis of PK was a secondary endpoint and was conducted only in peramivir-treated subjects with sufficient blood samples collected for inclusion in the PK analysis.

Bilateral mid-nasal swab specimens were collected for virologic analysis from all enrolled subjects at baseline (pre-dose) and on Days 3, 7, and where possible on Day 14. Virology laboratory tests included viral subtype characterization from the baseline sample, laboratory culture and analysis by $TCID_{50}$, and RT-PCR assay. Influenza virus isolates were also assessed for susceptibility to NAIs (Day 1 and last specimen yielding influenza virus on culture). A central laboratory performed all virologic assessments.

Safety assessments included monitoring of adverse events (AEs), laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, and physical examinations (see Section 8). Safety analyses were conducted in the Safety Population and were the primary endpoint. All randomized subjects who received at least one dose of study drug were included in the Safety Population.

Effectiveness was evaluated through assessments of time to alleviation of symptoms (TTAS), time to resolution of fever (TTRF), usage of antipyretic medications, incidence of influenza-related complications, ability to perform usual daily activities, appetite/eating patterns, and virologic outcomes (i.e., influenza virus titers, RT-PCR results, and virus susceptibility to neuraminidase inhibitors). TTAS was defined as the time from initiation of study drug to the time-point where all symptoms of influenza were "0 = none" or "1 = mild" for at least 21.5 hours (i.e., 24 hours minus 10%). TTRF was defined as the time from initiation of study drug to the time-point when the subject had an oral temperature of <99.4°F or an axillary temperature of <98.4°F and no antipyretic medications were taken for ≥12 hours. TTAS and TTRF were estimated by Kaplan-Meir method; subjects who did not achieve the endpoint were censored at the time of their last non-missing assessment. The protocol-specified influenza-related complications were otitis media, sinusitis, bronchitis, and pneumonia requiring antibiotic use, and were diagnosed by the investigator after initiation of study treatment based on physical examination. The efficacy analyses were secondary endpoints and were conducted in the Intent-to-Treat Infected (ITTI) Population, which included all randomized subjects who received at least one dose of study drug and had confirmed influenza A or B infection by RT-PCR.

Subject Disposition, Demographics and Baseline Characteristics

Study 305 enrolled a total of 137 subjects (peramivir 114, oseltamivir 23) at 12 sites in the U.S. and South Africa. Of these, 7 subjects randomized to IV peramivir were not treated; the Safety Population was therefore 130 subjects. An additional 34 subjects were not confirmed to have influenza infection; thus, the ITTI population was 97 subjects (peramivir 80, oseltamivir 16).

A total of 21 subjects were randomized in the ≥28 days to <2 years cohort. All but 1 subject had onset of illness ≤48 hours from screening (Subject (b) (6), a 16-month-old male infant, presented within 52 hours of onset of symptoms). The study completion rate in this cohort was 90%; two (10%) of 20 subjects randomized to IV peramivir prematurely discontinued the study prior to receiving study drug (1 subject had consent withdrawn shortly after randomization and the other had consent withdrawn after IV placement attempt was unsuccessful). The one subject randomized to oseltamivir completed the study. The Safety Population, therefore, consisted of 19 subjects (peramivir 18, oseltamivir 1). Seven additional subjects were not confirmed to have influenza by RT-PCR, including all 6 subjects enrolled at Site (b) (6) in South Africa; thus, the ITTI Population was 12 subjects (peramivir 11, oseltamivir 1).

> ***Reviewer comment:*** *When asked to account for the imbalance in PCR-confirmed influenza at Site (b) (6) compared with U.S. sites, the Applicant responded (NDA 206426 submission number [SN] 125) that the version of the protocol (Version 6.0, dated November 5, 2018) in effect during the 2019 influenza season in South Africa permitted enrollment of subjects based on clinical signs and symptoms provided that sponsor approval had been obtained. However, the training slides used for the initiation of Site (b) (6) erroneously omitted the protocol-specified requirement for sponsor approval to support enrollment based on clinical symptoms. Thus, the site enrolled subjects in good faith based on clinical symptoms that were not subsequently confirmed by RT-PCR. (Of note, two subjects at Site (b) (6) had a RAT at screening; one was negative and the other was positive for influenza B, which was not confirmed by RT-PCR). The Applicant attested that no items of concern were noted during routine monitoring of Site (b) (6) that would impact the integrity or reliability of the data generated therein. Safety data from the*

6 subjects treated with IV peramivir at Site (b) (6) will therefore be included in the FDA analyses of safety, but these subjects will be excluded from all effectiveness analyses.

There were 20 protocol deviations reported in 13 subjects in the ≥28 days to <2 years cohort (all in the peramivir group). None were considered important (defined as deviations which jeopardize the completeness, accuracy, or reliability of the study data or significantly affect a subject's rights, safety, or well-being) and most were minor. Major deviations in this age cohort pertained to the informed consent process (3 subjects) and dosing (2 subjects, both at Site (b) (6)). Regarding the dosing deviations at Site (b) (6), in both cases (Subjects (b) (6) and (b) (6)), the correct dose of peramivir was diluted in saline up to 25 mL; however, this dilution should have been made up to 100 mL based on the subjects' ages (15 months old in both cases). None of the protocol deviations were expected to impact subject safety or the interpretation of results.

Subject demographics and baseline disease characteristics for the ITTI population of the ≥28 days to <2 years cohort are listed in Table 4. In the peramivir group, the majority of subjects were female, White, and non-Hispanic, with a median age of 16 months and a baseline mean (SD) influenza composite symptom score of 4.8 (1.5); the maximum possible score for this age group was 15. Consistent with the inclusion criteria, none of the subjects had any significant medical history. Nearly all subjects (91%) presented within 48 hours of illness onset. The majority (64%) did not have a RAT at screening and were enrolled on the basis of symptoms. In the peramivir group, 55% of subjects were confirmed to be infected with influenza A/H3N2 by RT-PCR.

Table 4: Subject Demographics and Baseline Characteristics (ITTI Population, 28 Days to 2 Years Cohort)

		28 Days to 2 Years Age Cohort (N=12)	
		Peramivir	**Oseltamivir**
N		11	1
AGE (months)	Mean (SD)	14.2 (5.6)	11
	Min, Max	5, 22	
	Median	16	
GENDER, n (%)			
Female		7 (64)	1 (100)
Male		4 (36)	0
RACE, n (%)			
White		9 (82)	1 (100)
Black or African American		2 (18)	0
ETHNICITY, n (%)			
Hispanic or Latino		2 (18)	1 (100)
Not Hispanic or Latino		9 (82)	0
COUNTRY, n (%)			
United States		11 (100)	1 (100)
RAPID ANTIGEN TEST, n (%)			
Positive for Influenza A		3 (27)	0
Positive for Influenza B		1 (9)	1 (100)
Missing		7 (64)	0

INFLUENZA CONFIRMED BY RT-PCR, n (%)			
A/H1N1		3 (27)	0
A/H3N2		6 (55)	0
A/H3N2+B		1 (9)	0
B		1 (9)	1 (100)
TIME FROM SYMPTOM ONSET, n (%)			
0 to 12 hours		2 (18)	0
12 to 24 hours		1 (9)	1 (100)
24 to 36 hours		5 (45)	0
36 to 48 hours		2 (9)	0
> 48 hours		1 (9)	0
BASELINE COMPOSITE SYMPTOM SCORE[a]	Mean (SD)	4.8 (1.5)	4
	Min, Max	3, 7	
	Median	5	

Abbreviations: ITTI = Intent to Treat Infected; max = maximum; min = minimum; SD = standard deviation.
[a] Baseline composite symptom score was defined as the sum of the age-appropriate symptoms where, for each symptom, absent = 0; mild = 1; moderate = 2; severe = 3. The maximum possible composite score for subjects ≥ 28 days to < 2 years was 15.
Source: Reviewer-generated using ADSL and ADSS datasets

Treatment Compliance

Per protocol, subjects in Study 305 were to receive either a single infusion of IV peramivir or oral oseltamivir dosed BID × 5 days. All subjects in the ITTI population of the ≥ 28 days to < 2 years cohort completed their assigned study treatment.

Parents/caregivers for this age cohort completed the subject diaries for a mean of 10 days. The majority of caregivers completed the subject diaries through Day 8; thereafter, the completion rates dropped by more than half, and by Day 14, only 17% of subject diaries were completed. This reduction in the diary completion rate appeared to follow the resolution of fever, alleviation of influenza symptoms, and return to normal activities, both for this cohort and for Study 305 overall.

Analysis of Effectiveness Endpoints

- *Time to Alleviation of Symptoms and Resolution of Fever*

In the ≥28 days to <2 years cohort, the median time to alleviation of symptoms (TTAS) for the ITTI population was 76.3 hours in the peramivir group (n=10) and 98.6 hours in oseltamivir group (n=1). The median time to resolution of fever (TTRF) was 34.8 and 61.8 hours in the peramivir and oseltamivir groups, respectively.

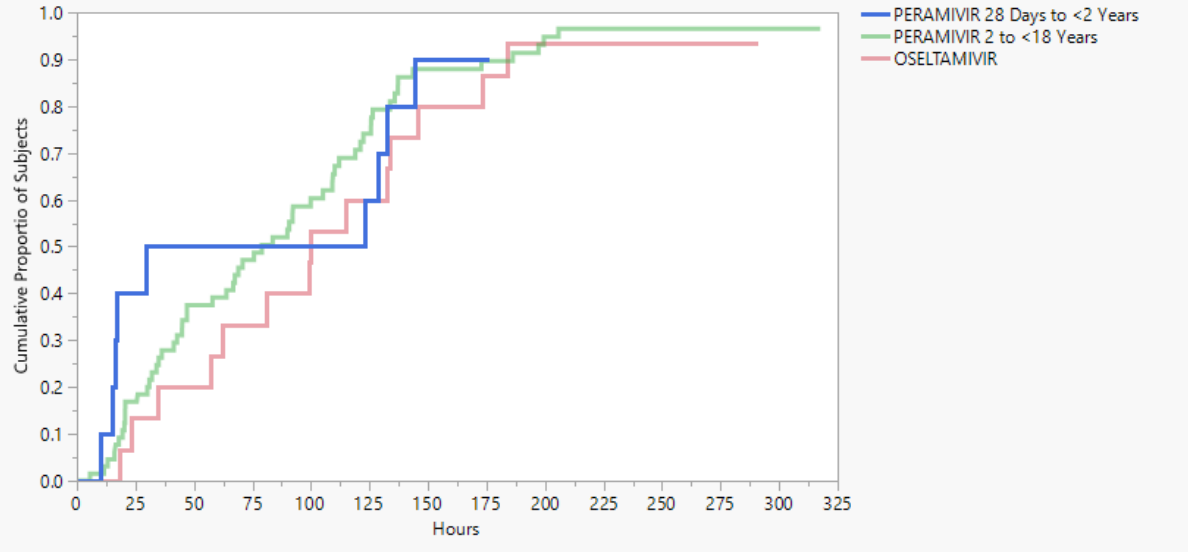
Although the number of influenza symptoms assessed daily for the TTAS endpoint differed between the youngest and older age cohorts (see Table 3), the median TTAS in the peramivir ≥28 days to <2 years old cohort was nonetheless consistent with that reported for peramivir-treated subjects ≥2 years old, and numerically lower than that reported for oseltamivir-treated subjects, as shown in Table 5 and Figure 1. Similar trends were noted for the TTRF endpoint. Given the small sample size of this youngest age cohort, subgroup analyses by viral subtype were not performed for these endpoints.

Table 5: Time to Alleviation of Symptoms and Time to Resolution of Fever Kaplan-Meier Estimate (ITTI Population)

	Peramivir			Oseltamivir
	28 Days to <2 Years (N=11)	2 to <18 Years (N=70)	Total (N=81)	Total (N=16)
Time to Alleviation of Symptoms (hours)				
N (number censored)	10 (1)	65 (6)	75 (7)	15 (1)
Mean (SD)	76.1 (19.8)	86.3 (7.3)	85.8 (6.9)	102.9 (14.6)
Median	76.3	79.0	79.0	99.8
95% CI	9.9, 132.7	47, 105.2	47, 109.2	34.7, 133.6
25% - 75%	16.6 – 132.7	34.9-125.6	30.9-126.4	57.3-145.3
Min, Max	9.9, 176	5.6, 317.6	5.6, 317.6	18.4, 290.6
Time to Resolution of Fever (hours)				
N (number censored)	10 (0)	57 (1)	67 (1)	13 (0)
Mean (SD)	39.7 (6.6)	46.9 (4.4)	45.9 (3.9)	34.8 (6.7)
Median	34.8	40.4	40.0	34.7
95% CI	21.1, 53.8	28.2, 47.0	28.2, 46.8	13.7, 42.3
25% - 75%	23.2 – 53.8	19.4 – 68.9	20.7 – 67.5	16.0-42.3
Min, Max	21.1, 87.0	1.5, 269.6	1.5, 269.6	2.9, 87.8

Abbreviations: max = maximum; min = minimum; SD = standard deviation
Note: 7 and 17 subjects overall were excluded from the Time to Resolution of Symptoms and Time to Resolution of Fever summaries, respectively, due to missing data or events resolving prior to initiation of study drug. Subjects who did not achieve the endpoint were censored at the time of their last non-missing assessment.
Source: Reviewer-generated using ADTTE dataset

Figure 1: Kaplan Meier Plot of Time to Alleviation of Symptoms (ITTI Population)



Source: Reviewer-generated using ADTTE dataset

With respect to the usage of antipyretic medications, a secondary endpoint, the mean (SD) number of doses used in the ≥28 days to <2 years old ITTI population was 4 (2.6) doses (range: 2-9 doses) in the peramivir group (n=11) and 7 doses in the 1 subject treated with oseltamivir. In the peramivir group, both the number of subjects receiving antipyretic medications and the mean number of doses

used decreased from Day 1 to Day 8; no subjects received antipyretic medications after Day 8. The oseltamivir subject did not receive any antipyretic medications after Day 3. There were no differences between this and the older age cohorts of Study 305 with respect to the mean number of antipyretic doses taken during the trial.

- *Influenza-related Complications*

Subjects in Study 305 were evaluated for the presence of the following influenza-related complications after initiation of treatment: sinusitis, otitis media, bronchitis and pneumonia requiring antibiotic usage. N no such cases were reported in the ≥28 days to <2 years old cohort.

- *Daily Activities, Appetite and Eating Patterns*

Overall, a favorable clinical effect was observed in both treatment groups for the assessments of usual daily activities and appetite/eating patterns. In the ≥28 days to <2 years old cohort, the median ability to perform daily activities reached the maximum score (10) by Days 6 and 9 in the peramivir and oseltamivir groups, respectively. All subjects in this cohort had appetite/eating patterns improved from abnormal or reduced to normal by Day 9. These trends were not noticeably different than in the older age cohorts, nor were there any differences seen by treatment group overall.

Conclusions on the Substantial Evidence of Effectiveness

The clinical outcomes data of Study 305 indicated that treatment with single-dose IV peramivir 12 mg/kg in pediatric subjects aged 6 months to 2 years old with acute uncomplicated influenza was associated with alleviation of symptoms and resolution of fever on a time-course comparable to that observed in older children treated with IV peramivir or in children treated with oral oseltamivir. In addition, no significant age- or treatment-related differences were noted with respect to antipyretic medication usage, return to normal activities, or return to normal appetite/eating patterns. Importantly, there were no influenza-related complications reported in the youngest age cohort. While the above comparisons were not conducted with any statistical rigor, the finding that the trends in clinical outcomes in subjects <2 years old treated with IV peramivir were in line with those observed for the overall study population is reassuring regarding the drug's effectiveness in this age group.

8. Safety

Adequacy of Drug Exposure Experience

The safety database for this supplement consists of clinical data from 19 subjects (peramivir 18, oseltamivir 1) in the ≥28 days to <2 years cohort of Study 305. This safety population is larger than the ITTI population due to the addition of 7 subjects who received a dose of peramivir but were not confirmed to be infected with influenza, including all 6 subjects from Site (b) (6) in South Africa. As noted in Section 7, the Applicant attested that safety data from this site were reliable and should not be excluded from the analyses.

Subjects in the peramivir treatment group received a single IV dose of peramivir at 12 mg/kg; the duration of exposure was 1 day. The one subject treated with oseltamivir received the standard 10 doses administered as 1 dose twice daily, for an exposure duration of 6 days. Subject demographics

and baseline characteristics in the Safety Population (Table 6) were not markedly different than in the ITTI Population, except for the greater representation of Black subjects.

Table 6: Subject Demographics (Safety Population, 28 Days to 2 Years Cohort)

		28 Days to 2 Years Age Cohort (N=19)	
		Peramivir	**Oseltamivir**
N		18	1
AGE (months)	Mean (SD)	14.6 (5.5)	11
	Min, Max	5, 23	
	Median	16	
GENDER, n (%)			
Female		11 (61)	1 (100)
Male		7 (39)	0
RACE, n (%)			
White		9 (50)	1 (100)
Black/African American		8 (44)	0
Asian		1 (6)	0
ETHNICITY, n (%)			
Hispanic or Latino		2 (11)	1 (100)
Not Hispanic or Latino		16 (89)	0
COUNTRY, n (%)			
United States		12 (67)	1 (100)
South Africa		6 (33)	0
BMI (kg/m^2)	Mean (SD)	18.6 (10.1)	15.5
	Min, Max	12.6, 58.4	
	Median	16.5	
WEIGHT (kg)	Mean (SD)	9.4 (1.6)	9
	Min, Max	6.6, 11.5	
	Median	10.1	
HEIGHT (cm)	Mean (SD)	73.8 (10.4)	76.2
	Min, Max	42.4, 88.9	
	Median	74.35	
eGFR (mL/min/1.73 m^2)	Mean (SD)	123.5 (33.9)	105
	Min, Max	44, 184	
	Median	125	

Abbreviations: BMI = body mass index; eGFR= estimated glomerular filtration rate; max = maximum; min = minimum; SD = standard deviation.
Source: Reviewer-generated using ADSL dataset and eGFR values submitted to NDA 206426 (SN 136)

Adequacy of Clinical Safety Assessments

Routine clinical testing in Study 305 consisted of both clinical and laboratory evaluations. Clinical evaluations occurred at Screening/ Day 1 and Days 3, 7, and 14. Laboratory evaluations (chemistry, hematology, and urinalysis) occurred on Days 1 and 7. Adverse events (AEs) were mapped according to the Medical Dictionary for Regulatory Activities (MedDRA) v18.0. All AEs and laboratory abnormalities were graded for severity according to the Division of AIDS (DAIDS)

Table for Grading Adverse Events for Adults and Pediatrics (December 2004; Clarification, 2009). These safety assessments were considered adequate.

Key Safety Results

There were no deaths or serious adverse events (SAEs) in Study 305. In the ≥28 days to <2 years cohort, three (17%) subjects in the peramivir group experienced 4 treatment-emergent adverse events (TEAEs): rhinorrhea (Subject (b) (6)), gastroenteritis (Subject (b) (6)), and diarrhea and vomiting (Subject (b) (6)). All of these AEs were reported as mild and, except for the event of rhinorrhea, all resolved during follow-up. Moreover, none of these AEs was considered related to peramivir or resulted in drug discontinuation. The sole subject in the oseltamivir group had no AEs.

> ***Reviewer comment:*** *In Study 305 as a whole, 21% of the safety population (n=130) experienced at least 1 TEAE (peramivir 22/107 [21%], oseltamivir 5/23 [22%]). No TEAE was reported by more than 5% of subjects in any given treatment group. Overall, the most frequently reported TEAE was vomiting (5% total; peramivir 4%; oseltamivir 9%). The incidence of vomiting considered related to peramivir, was slightly lower at 3% (versus 9% in the oseltamivir group). A higher percentage of subjects in the oseltamivir group (13%) compared with the peramivir group (5%) experienced TEAEs in the SOC of GI disorders. In contrast, more subjects in the peramivir group experienced TEAEs in the SOC of general disorders and administration site conditions (5% vs. 0, respectively). Consistent with the drug's route of administration, three (3%) subjects in the peramivir group experienced injection site reactions; however, none of these were in the ≥28 days to <2 years cohort.*

With respect to clinical laboratory evaluations, median values at Day 7 for clinical chemistry or hematology assessments in the ≥28 days to <2 years cohort were not notably different compared with baseline values. In the peramivir group, 9 (50%) subjects had treatment-emergent laboratory toxicities at Day 7, defined as at least 1 grade higher than recorded at baseline (for this analysis, only subjects with a given laboratory assessment at both baseline and Day 7 were counted). Six (33%) subjects had shifts in chemistry toxicity grade and 3 (20%) subjects had shifts in hematology toxicity grade. As shown in Table 7, the majority of these shifts were Grade 1 (i.e. from normal at baseline to Grade 1 at Day 7); toxicity shifts of Grade 2 or greater are discussed below. The sole subject in the oseltamivir group did not experience any treatment-emergent laboratory toxicities.

Table 7: Laboratory Toxicity Grade Shifts from Baseline to Day 7 (Safety Population, Peramivir Group, 28 Days to 2 Years Cohort)

Laboratory Parameter	Peramivir 28 Days to 2 Years Age Cohort (N=18)			
	Number (%) of Subjects[a]			
	Grade 1	Grade 2	Grade 3	Grade 4
CHEMISTRY (N=18[b])				
Albumin (g/dL) – low	0	1 (6)	0	0
Bicarbonate (mEq/L) – low	1 (6)	0	0	0
Calcium (mg/dL) – high	1 (6)	0	0	0
Glucose (mg/dL) – low	1 (6)	0	0	0
Potassium (mEq/L) – high	0	1 (6)	0	0
Sodium (mEq/L) – low	1 (6)	0	0	0
HEMATOLOGY (N=15[b])				
Hemoglobin (g/dL) – low	0	1 (7)	0	0

Neutrophils (10^3/uL) – low	1 (7)	0	2 (13)	0

[a] Percentages are based on the number of subjects with a given laboratory assessment at both Baseline and Day 7.
[b] N= the number of subjects with both baseline and Day 7 values reported.
S*ource: Reviewer-generated using ADLB dataset*

Two peramivir-treated subjects in the ≥28 days to <2 years cohort experienced Grade 2 toxicity shifts in chemistry assessments but neither of these findings were considered clinically significant by the investigator:

- Subject (b) (6) (S. Africa): a 6-month old boy, not confirmed to be infected with influenza, had a normal baseline potassium value of 4.6 mEq/L (normal range: 4.1-5.3 mEq/L) but developed a high potassium value of 6.2 mEq/L (Grade 2) at Day 7. No AEs or other treatment-emergent laboratory toxicities were reported; however, the subject had Grade 2 low serum bicarbonate and Grade 1 low serum sodium at both baseline and Day 7. No subsequent potassium values were reported for the subject.

- Subject (b) (6) (S. Africa): a 15-month old girl, not confirmed to be infected with influenza, had a Grade 1 low serum albumin of 3.1 g/dL (normal range: 3.8-5.4 g/dL) at baseline and Grade 2 low serum albumin of 2.9 g/dL at Day 7. No AEs or other treatment-emergent laboratory toxicities were reported, but the subject had Grade 1 low hemoglobin at both baseline and Day 7. No subsequent serum albumin values were reported for the subject.

Reviewer comment: *This reviewer agrees that the above laboratory abnormalities were not likely clinically significant. They were also unlikely related to peramivir administration. Of note, both cases came from the same South African site. The first case may represent laboratory error, while the second case may be reflective of poor nutritional intake.*

Three peramivir-treated subjects in the ≥28 days to <2 years cohort experienced Grade 2-3 toxicity shifts in hematology assessments. None of these findings were considered clinically significant by the investigators.

- Subject (b) (6) (S. Africa): a 19-month-old girl, not confirmed to be infected with influenza, with baseline hemoglobin concentration of 11 g/dL (normal range: 11.1-14.1 g/dL) developed a low hemoglobin value of 9.9 g/dL (Grade 2) at Day 7. No AEs were reported, but the subject had Grade 1 treatment-emergent low serum glucose at the Day 7 visit as well. In addition, the subject had the following abnormal chemistry values at baseline: Grade 2 high serum potassium and Grade 1 low serum bicarbonate and low sodium. No subsequent hemoglobin values were reported for the subject.

- Subject (b) (6) (U.S.): an 18-month old girl, with confirmed influenza A/H3N2+B infection, had a normal baseline neutrophil count of 4.8 x10^3/uL (normal range: 1.5-8.5 x10^3/ uL) but developed a low neutrophil count of 0.7 x10^3/ uL (Grade 3) at Day 8. No AEs or other treatment-emergent laboratory toxicities were reported, but the subject had the following abnormal hematology values at baseline: lymphocyte count 1.1 K/uL (normal range: 3.0-9.5 K/uL), lymphocytes percentage 16% (normal range: 45-73%), monocyte percentage 13% (normal range: 1-9%), and neutrophil percentage 71% (normal range: 18-48%). At the Day 8 visit, her lymphocyte count and monocyte percentage had returned to

normal ranges, but her lymphocyte percentage had risen to 79% (high) and her neutrophil percentage had fallen to 12% (low). None of these lab abnormalities were considered clinically significant and the subject developed no complications of influenza. No subsequent neutrophil counts were reported for the subject.

- Subject (b) (6) (U.S.): an 8-month old boy, with confirmed influenza A/H3N2 infection, had a normal baseline neutrophil count of 3.7 $x10^3$/uL (normal range: 1.5-8.5 x103/ uL) but developed a low neutrophil count of 0.6 $x10^3$/ uL (Grade 3) at Day 7. No AEs or other treatment-emergent laboratory toxicities were reported, but the subject had the following abnormal hematology values at baseline: hematocrit 41.7% (normal range: 33-39%), hemoglobin concentration 14.1 g/dL (normal range: 10.5-13.5 g/dL), lymphocyte count 2.0 K/uL (normal range: 3.0-9.5), lymphocyte percentage 31% (normal range: 45-73%), monocyte percentage 11% (normal range: 1-9%), and neutrophil percentage 57% (normal range: 18-48%). At the Day 7 visit, his lymphocyte count and monocyte percentage had returned to normal ranges, but his hematocrit and hemoglobin concentration remained slightly elevated (41.4% and 14.1 g/dL, respectively). In addition, his Day 7 lymphocyte percentage had risen to 79% and his neutrophil percentage had fallen to 7%. None of these lab abnormalities were considered clinically significant and the subject developed no complications of influenza. No subsequent neutrophil counts were reported for the subject.

Reviewer comment: *This reviewer concurs that the above abnormalities were not likely clinically significant. In the first case, the subject had low hemoglobin concentration at baseline; the subsequent Day 7 value likely represents a continuation of the same process and not likely due to peramivir administration. The cause of the treatment-emergent neutrophilia in the other two cases is not clear, but may be related to acute inlfuenza infection. Abnormal low neutrophil counts were also seen in the older cohorts of Study 305, with no discernable age-related trends, and in the adult trials of peramivir. Low neutrophil count is currently listed as an adverse reaction in Rapivab labeling (Section 6.1).*

With respect to urinalysis assessments, there were no shifts in urine erythrocytes reported in Study 305, and no shifts from baseline to graded protein abnormalities in the ≥28 days to <2-year-old cohort. In the older age cohorts, shifts from baseline to graded urine protein abnormalities occurred at a similar rate in the peramivir and oseltamivir groups.

Lastly, mean decreases in heart rate and respiratory rate from baseline were reported in the ≥28 days to <2-year-old cohort at each follow-up visit, which were not considered clinically significant and may possibly have been related to resolution of influenza illness among those with confirmed infection. No notable changes in systolic or diastolic blood pressure were observed. In Study 305 as a whole, there were no apparent treatment-related or age-related trends in vital sign changes from baseline. The change from baseline in body temperature is discussed as an effectiveness variable in Section 7.

Conclusions on Safety

Intravenous peramivir administered to pediatric subjects 6 months to 2 years of age in Study 305 was safe and well tolerated. There were no deaths, SAEs, AEs considered related to study drug, or AEs leading to drug withdrawal. There were a small number of treatment-emergent AEs and

laboratory toxicities reported in the peramivir group, but all were either mild or not clinically significant. Importantly, no new toxicities or infusion reactions were observed in this age cohort. Overall, the safety profile of IV peramivir in children ≥6 months old is favorable.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this pediatric supplement.

10. Pediatrics

The information contained in this sNDA was presented before the Pediatric Review Committee (PeRC) on December 8, 2020. The committee agreed that the submission partially fulfilled PREA PMR 2831-1. In addition, the PeRC agreed to grant a deferral extension to study IV peramivir in pediatric patients from birth to 6 months of age, as the need for a parenterally administered anti-influenza drug in this age group is recognized. However, given the recruitment challenges encountered in Study 305, which is now closed, the study of IV peramivir in neonates and young infants will likely require a different treatment setting. (b) (4)

11. Other Relevant Regulatory Issues

See the Appendix for clinical investigator financial disclosures related to the submitted clinical study.

12. Labeling

Prescribing Information

Below is a high-level summary of the critical changes made to the Rapivab prescribing information (PI) based on this sNDA; refer to the final approved labeling for full details.

- INDICATIONS AND USAGE:
  - The indication has been revised to include patients 6 months and older.
  - No changes to the existing Limitation of Use are proposed.
- DOSAGE AND ADMINISTRATION:
  - The dosage recommendations for pediatric patients have been updated to include patients 6 month and older (2.1).
  - A statement regarding the lack of data in inform dosage adjustment in pediatric patients 6 months to 2 years of age with creatinine clearance less than 50 mL/min has been added (2.2).

- A new table (**Table 3**) has been added to provide the recommended maximum infusion volumes by age and weight to ensure that volumes administered in the youngest age groups are within USP endotoxin limits (2.3).

Table 3. Maximum Infusion Volume by Age and Weight

Age	Weight (kg)	Maximum Infusion Volume* (mL)
Infants 6 months to 1 year of age	Any	25 mL
Adults and pediatric patients 1 year and older	5 kg to less than 10 kg	25 mL
	10 kg to less than 15 kg	50 mL
	15 kg to less than 20 kg	75 mL
	At least 20 kg	100 mL

*Infusion volume is the total volume of RAPIVAB 10 mg/mL solution and diluent. The final concentration of diluted RAPBIVAB for administration should be between 1 mg/mL and 6 mg/mL.

- ADVERSE REACTIONS:
  - The pediatric subsection has been updated to reflect adverse reactions observed for the entire Safety Population of Study 305 in subjects 6 months to 17 years of age (6.1).
- USE IN SPECIFIC POPULATIONS:
  - The pediatric subsection (8.4) has been updated to incorporate the changes made to Sections 1, 2.2, 2.3, and 6.1.
- CLINICAL PHARMACOLOGY:
  - A new table (Table 5) has been added to describe the geometric mean (%CV) C_{max} and AUC_{0-3} values for each pediatric age cohort in comparison to adults. Language was added to state that the observed difference in exposure between pediatric patients 6 months to less than 2 years of age and adults is not considered to be clinically significant (12.3).
  - New amino acid substitutions associated with reduced susceptibility to peramivir based on isolates from clinical trials or community surveillance studies have been added to Table 7. In addition, a new table (Table 8) has been added to describe the amino acid substitutions observed in influenza A/H5N1 and A/H7N9 clinical isolates that conferred reduced susceptibility to peramivir in biochemical assays (12.4).
- CLINICAL STUDIES:
  - Results from Study 305 have been updated to reflect the expanded ITTI population of all subjects 6 months to 17 years of age (14.2). The section provides a fair representation of the clinical outcomes following administration of IV peramivir under the recommended conditions of use, and is neither misleading, inaccurate, or promotional.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

Not applicable.

Appendix

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 206426/S-007
Submission Date(s): July 29, 2020
Applicant: BioCryst Pharmaceuticals, Inc.
Product: Rapivab® (peramivir) for injection

Reviewer: Peter Miele, MD
Date of Review: January 20, 2021
Covered Clinical Study (Name and/or Number): Study BCX1812-305

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 11		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant adequately disclosed financial interests/arrangements for all investigators who enrolled subjects into Study BCX1812-305. Clinical investigators were certified regarding the absence of financial interests and arrangements per requirements in 21 CFR 54.4(a)(1).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER S MIELE
01/28/2021 12:45:07 PM

WENDY W CARTER
01/28/2021 01:32:45 PM