Combined Clinical, Statistical and Cross-Discipline Team Leader Review

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Proprietary Name / Established (USAN) names	Rapivab; Peramivir injection
Dosage forms / Strength	200 mg (20 mL) vial for injection
Proposed Indication(s)	Treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than two days
Recommended:	Approval

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1. Introduction

This review summarizes the data used to support BioCryst's supplemental NDA seeking approval for the use of Rapivab® (peramivir injection) for intravenous (IV) use for the treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days. Peramivir is an influenza virus neuraminidase inhibitor that provides antiviral activity by inhibiting influenza virus neuraminidase enzyme necessary for releasing viral particles from infected cells.

Peramivir is currently approved in the United States as a single intravenous dose for the treatment of acute uncomplicated influenza in adults (≥18 year of age) who have been symptomatic for no more than two days. Efficacy for the approved indication was demonstrated in adequate and well-controlled clinical trials of naturally occurring influenza in adults, in which the predominant influenza infections were influenza A. An insufficient number of subjects infected with influenza B virus were enrolled in the pivotal trials to determine efficacy for this influenza type.

This supplemental NDA was submitted by BioCryst Pharmaceuticals, Inc. to support inclusion of patients 2 years of age and older in the approved indication. The submission contains interim pharmacokinetic (PK), safety, and efficacy outcomes data from an ongoing Phase 3 trial, Study BCX1812-305, of IV peramivir in subjects aged 2 to <18 years with acute uncomplicated influenza. Study BCX1812-305 is a randomized, multicenter, open-label, active-controlled trial in which pediatric subjects are randomized to receive treatment with a single dose of IV peramivir or 5 days of oral oseltamivir administered within 48 hours of onset of influenza symptoms. The purpose of the trial is to evaluate safety of IV peramivir compared with oral oseltamivir. Secondary objectives are to describe PK in pediatric subjects and to evaluate the efficacy of IV peramivir compared with oral oseltamivir; however, the trial is not powered to formally test clinical outcome measures. Although other neuraminidase inhibitors are approved for the treatment of acute uncomplicated influenza in pediatrics patients, approval of this efficacy supplement would provide an additional, single-dose option for this age group.

2. Background

Peramivir injection under the trade name Rapivab® was approved in the United States on December 19, 2014, for the treatment of acute uncomplicated influenza in patients ≥18 years old who have been symptomatic for no more than two days. The current supplemental NDA was submitted to support inclusion of pediatric patients ≥2 years of age to the approved indication for peramivir. It contains an interim clinical study report for an ongoing open-label, active-controlled trial (Study BCX1812-305) currently being conducted to fulfill the Pediatric Research Equity Act (PREA) requirement issued in the original approval letter.

Table 2-1 summarizes the FDA-approved drugs for the treatment of influenza. Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are influenza virus neuraminidase inhibitor drugs approved for the treatment of acute uncomplicated influenza A and B infection in patients who

have been symptomatic for no more than two days. Pediatric patients aged ≥2 weeks and aged ≥7 years are included in the treatment indication for oseltamivir and zanamivir, respectively. Oseltamivir is available as capsules or liquid suspension for oral administration and zanamivir is available as powder for oral inhalation. Use of either drug for the treatment of acute uncomplicated influenza is intended for 5 days. The adamantane drugs are no longer recommended for the treatment of influenza due to widespread adamantane resistance among currently circulating influenza A strains and lack of activity against influenza B.

Table 2-1: FDA-Approved Drugs for the Treatment of Influenza

Drug Class	Activity	Generic Name	Trade Name	Approved Age Group
Neuraminidase Inhibitor	Influenza A and B	Oseltamivir phosphate	Tamiflu®	≥ 2 weeks
		Zanamivir	Relenza®	≥ 7 years[a]
		Peramivir	Rapivab®	≥18 years
Adamantane	Influenza A	Amantadine hydrochloride	Symmetrel®	≥ 1 years
		Rimantadine hydrochloride	Flumadine®	≥17 years

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

The U.S. Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) recommend the approved neuraminidase inhibitor drugs for the treatment of acute uncomplicated influenza. Per the CDC and AAP, antiviral treatment should be offered to children at high risk for influenza complications (i.e., <2 years old) and may be considered for any healthy child who can begin treatment within 48 hours from onset of illness.

The FDA's guidance document on the development of influenza drugs recommends sponsors conduct adequate and well-controlled trials to fulfill PREA requirements and extend treatment indications to pediatric age groups. Placebo-controlled trials, however, are no longer feasible because of established treatment guidelines. The pediatric study plan for Rapivab® was discussed with the FDA Pediatric Review Committee (PeRC) in August 2014. The committee acknowledged that placebo-controlled pediatric trials are no longer feasible and that a superiority trial would require large numbers of subjects. In addition, the short duration of treatment effect (1-2 days) observed with other influenza drug products precludes the ability to establish a meaningful non-inferiority margin for active-controlled trials. For these reasons, the PeRC and the review team agreed that partial extrapolation of efficacy from adult trials, with bridging PK and safety data in pediatric subjects, was an acceptable model moving forward for pediatric development. An open-label, active-controlled trial to evaluate PK, safety, and efficacy of IV peramivir in comparison to oral oseltamivir was considered a reasonable approach. Although such a trial would not be powered to formally test efficacy endpoints, trends in clinical outcomes would be compared with oseltamivir as well as to the adult data with peramivir. In addition, the trial would provide comparative safety data in a pediatric population.

3. CMC/Device

Currently, the only approved peramivir formulation is the 200 mg per 20 mL (10 mg/mL) solution in single-use vials for intravenous (IV) infusion. The marketed formulation was used

in Study BCX1812-305. The applicant did not present new chemistry or manufacturing information in this pediatric submission.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies were performed for peramivir and have been reviewed in prior submissions. No new nonclinical pharmacology/toxicology studies were submitted in the current sNDA.

5. Clinical Pharmacology/Biopharmaceutics

Analyses of the pharmacokinetic (PK) data are an important part of this supplemental NDA because efficacy might be extrapolated from adults if the pediatric PK exposures match the adult exposures deemed safe and effective. The subjects administered peramivir in Study BCX1812-305 had PK samples collected on Day 1 at the following time-points: immediately after completing peramivir infusion, between 30 minutes to 1 hour post-infusion, between 1 to 3 hours post-infusion, and between 3 to 6 hours post-infusion. The PK data observed in each age cohort was compared to the PK from healthy adults administered 600 mg of IV peramivir in Study BCX1812-113. By March 2017, a total of 87 subjects aged 2 to <18 years received IV peramivir and had sufficient blood samples collected for inclusion in the PK analysis. Eleven of these subjects, all of whom were between the age of 2 to <7 years, were included in the 90-Day Safety Update. A single peramivir-treated subject (Subject 020.007) in the 13 to <18 year-old cohort was not included in the PK analysis because no blood samples were collected.

The PK endpoints were $AUC_{0\text{-}3h}$ (area under the plasma concentration versus time curve from time zero to 3 hours post dose), AUC_{last} (AUC from time zero to the last measurable concentration), C_{max} (maximum observed plasma concentration), T_{max} (time to achieve C_{max}), and T_{last} (time of last measurable plasma concentration). $AUC_{0\text{-}3h}$ was used for comparison to the adult PK data because the truncated AUC value did not extrapolate beyond the measured concentrations collected during the study. The 3-hour time point was considered appropriate because all subjects in Study BCX1812-305 had a recorded T_{last} of approximately 3.5 hours.

Table 5-1 compares the geometric mean exposures ($AUC_{0\text{-}3h}$ and C_{max}) for each pediatric age cohort in Study BCX1812-305 with those observed in adults in Study BCX1812-113. Overall, peramivir exposures reported in the pediatric trial were similar to those seen in adults. Higher peramivir $AUC_{0\text{-}3h}$ exposures were observed in the 7 to <13 year-old cohort and lower exposures were observed in the 2 to <7 year-old and 13 to <18 year-old cohorts. The increased exposures within the 7 to <13 year-old cohort were not considered clinically relevant based on the favorable safety profile observed in this trial. The lower exposures within the other age cohorts were also not considered clinically relevant because the $AUC_{0\text{-}3h}$ known to be effective in adults is 53,900 ng•h/mL. Please refer to Clinical Pharmacology review by Simbarashe Zvada, Ph.D. for complete details.

Table 5-1: Geometric Mean Exposures (AUC_{0-3h} and C_{max}) in Pediatric Subjects from Study BCX1812-305 (Data Cutoff of March 2017) Compared to Adults from Study BCX1812-113

Age Groups	N	Mean Age (range)	Mean Dose (range)	Geometric Mean AUC_{0-3h} ng•h/mL (%CV)	Geometric Mean C_{max} ng/mL (%CV)
Overall (2 - <18 years)	87[a]	9.5 yrs (2.3–17.5)	408 mg (163–600)	69,400 (40.5)	54,200 (49.8)
2 - < 7 years	28[b]	5.0 yrs (2.3–6.7)	246 mg (163–474)	63,100 (40.0)	47,400 (48.9)
7 - < 13 years	39	9.6 yrs (7.2–12.2)	427 mg (256–600)	76,300 (43.1)	61,200 (53.0)
13 - < 18 years	20	15.9 yrs (13.1–17.5)	600 mg	65,500 (28.1)	51,500 (33.0)
Adults (Study BCX1812-113)	24	42 yrs (22–61)	600 mg	68,500 (19.1)	45,700 (21.5)

[a] N = 86 for AUC_{0-3h}
[b] N = 27 for AUC_{0-3h}
Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Tables 20 and 21; Clinical reviewer's calculations.

6. Clinical Microbiology

Study BCX1812-305 included virologic analyses to evaluate the antiviral activity of IV peramivir in pediatric subjects with acute uncomplicated influenza. Subjects had bilateral mid-nasal nasal swab specimens collected for virologic analyses at baseline (pre-dose), Day 3, Day 7, and, where possible Day 14. Virologic tests included viral subtype characterization from baseline samples, laboratory culture and viral titer analysis by $\log_{10}$ tissue culture infective dose 50% ($TCID_{50}$), reverse transcriptase polymerase chain reaction (RT-PCR) assay, viral susceptibility to neuraminidase inhibitors (peramivir, oseltamivir, and zanamavir), and genotypic analysis of primary virus isolates. The phenotypic and genotypic assays were performed on paired specimens collected at baseline and at the last post-baseline specimen with a positive virus culture (>0.5 $\log_{10}$ $TCID_{50}$/mL).

The virologic endpoints were to assess the change (reduction) in influenza virus titer by $\log_{10}$ $TCID_{50}$, change (reduction) in influenza viral loads by RT-PCR, and change in viral susceptibility to neuraminidase inhibitor drugs. The virologic analyses were conducted in all randomized subjects who received at least 1 dose of study drug and had laboratory-confirmed influenza infection denoted by a positive RT-PCR assay. By the data cutoff of March 2017, a total of 84 subjects between the age of 2 to <18 years had confirmed influenza infection. Of these, 69 subjects received peramivir treatment and 15 subjects received oseltamivir treatment.

Table 6-1 summarizes the proportion of subjects who had persistent viral shedding (i.e., positive viral titers) over time. A $\log_{10}$ $TCID_{50}$/mL value of >0.5 was considered a positive viral titer. The two treatment groups had similar percentages of subjects with positive viral titers over time, except at Day 3 where a lower percentage in the peramivir group compared with the oseltamivir group had positive titers (50% versus 75%, respectively). Among those administered peramivir, a greater percentage with influenza B compared to influenza A had

viral shedding at Day 3 (83% [B] versus 40% [A/H1N1] versus 8% [A/H3N2]). Only 3 of the peramivir-treated subjects, including 2 infected with influenza B and 1 co-infected with influenza A/H3N2 and B, had persistent viral shedding at Day 7. No subject from either treatment group had positive viral titers at Day 14. There were no meaningful differences across age cohorts with regards to viral shedding.

Table 6-1: Viral Shedding by Study Visit in Subjects with Positive Baseline Titers (>0.5 $\log_{10}$ $TCID_{50}$/mL) – Intent-to-Treat Infected Population (Data Cutoff of March 2017)

Study Visit	Peramivir	Oseltamivir	Total
Baseline	61/61 (100%)	13/13 (100%)	74/74 (100%)
Day 3	30/60 (50%)	9/12 (75%)	39/72 (54%)
Day 7	3/60 (5%)	0/12	3/72 (4%)
Day 14	0/60	0/12	0/72

Note: Six subjects overall were excluded due to a negative baseline titer value. A subject was considered to have a negative viral titer if his or her $\log_{10}$ $TCID_{50}$/mL value was ≤0.5.
Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Table 23; Clinical reviewer's calculations.

Table 6-2 summarizes the proportion of subjects who continued to have positive influenza results by RT-PCR over time. A RT-PCR result was considered positive if there was a detectable value ($\log_{10}$ vp/mL). The two treatment groups had similar percentages with positive influenza viral loads over time, with the exception of Day 7 where a lower percentage of subjects in the peramivir group compared with the oseltamivir group had detectable results (65% versus 93%, respectively). Similar percentages in the peramivir and oseltamivir groups had positive results at Day 14 (34% versus 29%, respectively). There were no meaningful differences across age cohorts or viral subtypes with regards to influenza results by RT-PCR.

Table 6-2: RT-PCR Results by Study Visit in Subjects with Positive Baseline Results (Detectable $\log_{10}$ vp/mL) – Intent-to-Treat Infected Population (Data Cutoff of March 2017)

Study Visit	Peramivir	Oseltamivir	Total
Baseline	69/69 (100%)	15/15 (100%)	84/84 (100%)
Day 3	66/68 (97%)	14/14 (100%)	80/82 (98%)
Day 7	46/68 (68%)	13/14 (93%)	59/82 (72%)
Day 14	23/68 (34%)	4/14 (29%)	27/82 (33%)

Note: The RT-PCR result was considered positive if there was a detectable value.
Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Table 23; Clinical reviewer's calculations.

By the March 2017 data cutoff, paired baseline/post-baseline phenotypic and genotypic assays were available for analysis in 30 (100%) of the peramivir-treated subjects and 8 (89%) of the oseltamivir-treated subjects who had positive post-baseline virus cultures (>0.5 $\log_{10}$ $TCID_{50}$/mL). All available post-baseline viruses from peramivir-treated subjects remained susceptible to peramivir, oseltamivir, and zanamivir. A single oseltamivir-treated subject with influenza A/H3N2 developed reduced susceptibility to oseltamivir, but no genotypic changes in neuraminidase or hemagglutinin genes were identified for that subject. No treatment-emergent mutations previously associated with reduced susceptibility to peramivir (i.e.,

H275Y substitution) were identified in any subject treated with peramivir or oseltamivir. Please refer to the clinical virology review by William Ince, Ph.D. for further details.

7. Clinical/Statistical- Efficacy

Efficacy Summary

The effectiveness of peramivir for the treatment of acute uncomplicated influenza in children 2 to <18 years of age is supported by partial extrapolation of efficacy from the adequate and placebo-controlled trials in adults and efficacy outcomes from a U.S. Phase 3, open-label, randomized, oseltamivir-controlled trial (Study BCX1812-305) conducted in pediatric subjects aged 2 to <18 years. In Study BCX1812-305, secondary efficacy endpoints included such outcomes as time to alleviation of influenza symptoms and time to resolution of fever. Overall, subjects 2 to <18 years of age treated with peramivir or oseltamivir had numerically comparable clinical outcome measures; however, the findings were not statistically significant. The interim data were limited and the trial was not powered to detect statistically significant differences between treatment groups. The median time to alleviation of influenza symptoms was 79 hours (interquartile range: 34-122 hours) in subjects receiving peramivir and 107 hours (interquartile range: 57-145 hours) in subjects receiving oseltamivir. The median time to recovery to normal temperature (less than 37°C) was 40 hours (interquartile range: 19-68 hours) and 28 hours (interquartile range: 15-41 hours) in subjects receiving peramivir and oseltamivir, respectively. No meaningful differences were observed between treatment groups in the use of antipyretic medications. A small number of subjects (N=4, 6%) in the peramivir group had protocol-specified influenza-related complications, but all cases resolved and none were serious events. Among subjects who received peramivir, no meaningful differences with regards to clinical outcomes were observed across the age cohorts or influenza virus subtypes.

7.1 Summary of Trial Design

Study BCX1812-305 is the pivotal trial submitted to support pediatric approval of IV peramivir for the treatment of acute, uncomplicated influenza in patients ≥2 years of age who have been symptomatic for no more than two days. The trial is an ongoing Phase 3, multi-center, open-label, randomized, active-controlled study designed to evaluate the safety, PK, and efficacy of IV peramivir in pediatric patients with acute uncomplicated influenza. This trial is being conducted in the U.S., and is evaluating the same population and dosing regimen proposed for labeling.

The primary objective of Study BCX1812-305 is to evaluate the safety of IV peramivir compared with oral oseltamivir in pediatric subjects with acute uncomplicated influenza. Key secondary objectives are 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.

Key inclusion criteria are age (28 days to 17 years inclusive), onset of symptoms ≤ 48 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 is known to be circulating in the community are considered to have clinical symptoms consistent with acute influenza infection. Fever has to be documented at the time of screening or reported by parent/caregiver if the subject received an antipyretic medication within 6 hours prior to the screening assessment. Enrolment at each site by clinical symptoms alone is approved by the Sponsor at the beginning of each influenza season once influenza was confirmed in the local community. The Sponsor can withdraw approval for symptomatic screening in any season based upon trends in influenza surveillance data.

Key exclusion criteria include subjects with complicated influenza (i.e., ICU care, evidence of organ dysfunction, proven/suspected concomitant bacterial infection, or other concomitant viral infection, like respiratory syncytial virus bronchiolitis), chronic disease/illness that may be an indicator of increased risk of influenza-related complications, or presence of immunocompromised status. Subjects are also excluded if they developed symptoms while hospitalized for another indication, received a live attenuated influenza vaccine within 14 days of presentation, or are pregnant or breast-feeding at screening.

Subjects are enrolled according to the following age-based cohorts: 28 days to <2 years old (up to 20 subjects), 2 to <7 years old (up to 40 subjects), 7 to <13 years old (up to 40 subjects), and 13 to <18 years old (up to 30 subjects). Enrolled subjects from each cohort are 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 is performed and sample sizes are not based on statistical considerations for detecting statistical differences.

The dose of IV peramivir administered in this trial is 12 mg/kg (maximum 600 mg) for subjects 2 to <13 years old and 600 mg for subjects ≥13 years old. The proposed peramivir dosing for children 2 to ≤12 years old is based on population PK modeling. The proposed peramivir dose for children ≥13 years old is the same as that approved for adults because children ≥13 years old are anticipated to achieve similar exposures as adults. Oseltamivir dosing is weight based for children 2 to ≤12 years old (30 mg BID if weight ≤15 kg, 45 mg BID if weight 15.1 - 23 kg, 60 mg BID if weight 23.1 – 40 kg, and 75 mg BID if weight >40 kg) and 75 mg BID for children ≥13 years old.

After initiating treatment with either IV peramivir or oral oseltamivir on Day 1, subjects undergo 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 are 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 7.1-1 summarizes the Subject Diary assessments and recording frequencies. Body temperature measurements are recorded until temperature normalizes for 48 hours without the use of antipyretic medication (i.e., temperature <99.4°F orally in children ≥6 years old and <98.4°F axillary in children <6 years old for 4 measurements). Assessments of age-specific signs and symptoms of influenza are recorded until symptom resolution and through the last follow-up visit (whichever comes

first). Assessments for antipyretic use (acetaminophen or ibuprofen), ability to perform usual activities, and appetite/eating patterns are recorded through the final follow-up assessment.

Table 7.1-1: Subject Diary Assessments

Assessment	Recording Frequency
Body Temperature (oral or axillary)[a]	Twice daily
Use of antipyretic medication (acetaminophen or ibuprofen)	Whenever applicable
Age specific signs & symptoms of influenza 28 days to < 4 years: 5 influenza symptoms[b] 4 to < 7 years: 7 influenza symptoms[c] 7 to < 18 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 and/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 to < 13 years old had the following 7 influenza symptoms assessed: cough, sore throat, nasal obstruction, myalgia (muscle aches), headache, feverishness, and fatigue)

After peramivir administration, subjects have single 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. The analysis of PK is a secondary endpoint of the trial, and conducted only in peramivir-treated subjects who have sufficient blood samples collected for inclusion in the PK analysis.

The safety assessments include monitoring of adverse events (AEs), laboratory analyses (clinical chemistry, hematology, and urinalysis), vital signs, and physical examinations. The safety analyses are conducted in the Safety Population and are the primary endpoints of the trial. All randomized subjects who received at least one dose of study drug are included in the Safety Population.

Efficacy is 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 is defined as the time from initiation of study drug to the time-point where all of the symptoms of influenza are “0: none” or “1: mild” for at least 21.5 hours (i.e., 24 hours minus 10%). TTAF is defined as the time from initiation of study drug to the time-point the subject has 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 are estimated by using the method of Kaplan-Meir; subjects who do not achieve alleviation of symptoms or resolution of fever are censored at the time of their last non-missing assessment.

The protocol-specified influenza-related complications are otitis media, sinusitis, bronchitis, and pneumonia requiring antibiotic use, and are diagnosed by the investigator after initiation of study treatment based on physical examination. The efficacy analyses are secondary endpoints and are conducted in the Intent-to-Treat Infected (ITTI) Population. The ITTI Population includes all randomized subjects who received at least one dose of study drug and had confirmed influenza A or B infection by RT-PCR.

The following noteworthy protocol changes were implemented after April 2016:

- Subjects <7 years old will no longer be randomized to oseltamivir
- The 2 to <7 year-old cohort will consist of up to 10 subjects aged 2 to <4 years and up to 30 subjects aged 4 to <7 years
- A new cohort will consist of 10 subjects from birth to <28 days old
- The peramivir dose for subjects <6 months old will be 8 mg/kg

This pediatric sNDA submission includes safety, efficacy, and PK data from 115 subjects age 2 to <18 years who enrolled between March 11, 2015 and March 31, 2017. By the end of April 2016, enrollment for the two oldest age cohorts was complete (≥7 to <13 years [n=48] and ≥13 to <18 years [n=30]), and 26 of the planned 40 subjects had enrolled in the ≥2 to <7 year-old cohort. The 90-day safety update submitted to this sNDA on June 23, 2017, included 11 additional subjects who enrolled in the 2 to <7 year-old cohort between May 1, 2016 and March 31, 2017. These subjects were not in the interim analysis, and included four subjects aged 2 to <4 years. By the end of March 2017, enrollment for the 2 to <4 year-old subgroup was complete and 27 of the planned 30 subjects had enrolled in the 4 to <7 year-old subgroup. Table 7.1-2 summarizes the number and percentage of enrolled subjects in each analysis population as of March 31, 2017.

Table 7.1-2: Analysis populations (Data Cutoff of March 2017)

Age Group	Peramivir	Oseltamivir	Total
Overall			
Intent-to-Treat Population[a]	N = 93	N = 22	N = 115
Safety Population[b]	88 (95%)	22 (100%)	110 (96%)
Intent-to-Treat Infected Population[c]	69 (74%)	15 (68%)	84 (73%)
Age 2 to <7 years			
Intent-to-Treat Population	N = 31	N = 6	N = 37
2 to <4 year-old subgroup	8 (26%)	2 (33%)	10 (27%)
4 to <7 year-old subgroup	23 (74%)	4 (67%)	27 (73%)
Safety Population	28 (90%)	6 (100%)	34 (92%)
2 to <4 year-old subgroup	6 (19%)	2 (33%)	8 (22%)
4 to <7 year-old subgroup	22 (71%)	4 (67%)	26 (70%)
Intent-to-Treat Infected Population	26 (84%)	3 (50%)	29 (78%)
2 to <4 year-old subgroup	5 (16%)	0	5 (14%)
4 to <7 year-old subgroup	21 (68%)	3 (50%)	24 (65%)
Age 7 to <13 years			
Intent-to-Treat Population	N = 39	N = 9	N = 48
Safety Population	39 (100%)	9 (100%)	48 (100%)
Intent-to-Treat Infected Population	30 (77%)	7 (78%)	37 (77%)
Age 13 to <18 years			
Intent-to-Treat Population	N = 23	N = 7	N = 30
Safety Population	21 (91%)	7 (100%)	28 (93%)
Intent-to-Treat Infected Population	13 (57%)	5 (71%)	18 (60%)

[a] Intent-to-Treat (ITT) Population included all subjects randomized.
[b] Safety Population included all randomized subjects who received ≥1 dose of study drug.
[c] Intent-to-Treat Infected (ITTI) Population included all subjects who were randomized, received study drug, and had confirmed influenza A or B by RT-PCR.
Source: Adapted from updated clinical study report tables and figures for Study BCX1812-305, Table 10; Clinical reviewer's calculations.

7.2 Demographics and Baseline Characteristics

A total of 115 subjects age 2 to <18 years enrolled into Study BCX1812-305 between March 11, 2015 and March 31, 2017. Subjects were enrolled at 10 U.S. sites. More than half were enrolled at three study sites, including 27%, 21%, and 17% by the investigators at sites No. 005, No. 020, and No. 008, respectively.

Table 7.2-1 summarizes the demographic characteristics of the 84 subjects who had confirmed influenza A or B infection by RT-PCR and received ≥1 dose of study drug (ITTI population). The ITTI population included 69 subjects (82%) treated with peramivir and 15 subjects (18%) treated with oseltamivir. The peramivir group consisted of 38 males (55%) and 31 females (45%). There were 6 males (40%) and 9 females (60%) in the oseltamivir group. Median ages were 7.9 years (range 2.3 to 17.4 years) and 10.4 years (range 3.0 to 17.7 years) for the peramivir and oseltamivir groups, respectively. In the peramivir group, 38%, 43%, and 19% of subjects were in the 2 to <7 year-old, 7 to <13 year-old, and 13 to <18 year-old cohorts, respectively. In the oseltamivir group, 20%, 47%, and 33% of subjects were in the 2 to <7 year-old, 7 to <13 year-old, and 13 to <18 year-old cohorts, respectively. Over 90% of subjects in either treatment group were white.

The majority of subjects in both treatment groups had confirmed influenza A infection by RT-PCR, particularly the H1N1 subtype (30%, peramivir group; 60%, oseltamivir group). Confirmed influenza B infection by RT-PCR was reported in 36% and 20% of the subjects in the peramivir and oseltamivir groups, respectively. Positive baseline viral titers (log_{10} $TCID_{50}$/mL value >0.5) were reported in most subjects in the ITTI population, including 88% in the peramivir group and 87% in the oseltamivir group. Median ability to perform daily activities was assessed as a 3 (on a scale of 0 to 10) in each treatment group. A similar proportion of subjects with abnormal or reduced appetite/eating patterns at baseline was observed in the peramivir (45/65 [69%] subjects) and oseltamivir (11/14 [79%] subjects) groups.

Table 7.2-1: Demographics by Treatment Group - Intent-to-Treat-Infected Population (Data Cutoff of March 2017)

Baseline Characteristics	Peramivir N=69	Oseltamivir N=15	Total N=84
Sex			
Male	38 (55%)	6 (40%)	44 (52%)
Female	31 (45%)	9 (60%)	40 (48%)
Age (years)			
Median (Q1–Q3)	7.9 (6.1–11.8)	10.4 (8.5–14.2)	8.4 (6.1–12.1)
Min, Max	2.3, 17.4	3.0, 17.7	2.3, 17.7
Age Group, n (%)			
2 - <7 years-old	26 (38%)	3 (20%)	29 (35%)
7 - <13 years-old	30 (43%)	7 (47%)	37 (44%)
13 - <18 years-old	13 (19%)	5 (33%)	18 (21%)
Race			
White	63 (91%)	15 (100%)	78 (93%)
Black or African American	6 (9%)	0	6 (7%)
Ethnicity			
Hispanic or Latino	18 (26%)	3 (20%)	21 (25%)
Not Hispanic/Latino	51 (74%)	12 (80%)	63 (75%)
Weight (kg)			
Median (Q1–Q3)	29.0 (19.8–46.4)	40.5 (27.3–59.3)	31.3 (21.1–53.9)
Min, Max	13.6, 111.9	13.4, 71.2	13.4, 111.9
Influenza type, n (%)			
A/H1N1	21 (30%)	9 (60%)	30 (36%)
A/H3N2	18 (26%)	3 (20%)	21 (25%)
A/Indeterminate	1 (1%)	0	1 (1%)
B	25 (36%)	3 (20%)	28 (33%)
A + B co-infection[a]	4 (6%)	0	4 (5%)
Viral titer[b], n (%)			
Positive	61 (88%)	13 (87%)	74 (88%)
Negative	8 (12%)	2 (13%)	10 (12%)

[a] Influenza A + B co-infection included those with influenza A/H1N1 + B (n=1), influenza A/H3N2 + B (n=2), and influenza A/Indeterminate + B (n=1).

[b] A subject was considered to have a positive titer if his/her log_{10} $TCID_{50}$/mL value was >0.5 and a negative titer if value ≤0.5.

Source: Adapted from interim clinical study report and 90-day safety update for BCX1812-305, demographic data Listing 16.2.4.3-90d and Tables 14.1.2.1.3-90d, 14.1.4.2.4, and 14.1.4.2.5; Clinical reviewer's calculations.

In sum, the majority of enrolled subjects in this trial were white, age 7 to <13 years, and had confirmed influenza A infection with positive viral titers. Median ability to perform daily activities and proportion of subjects with abnormal or reduced appetite/eating patterns were similar between treatment groups.

Demographics and Baseline Characteristics by Age Cohort

Table 7.2-2 summarizes the demographic characteristics for ITTI population by age cohort. As noted with the overall ITTI population, most of the subjects within each age cohort were white, had confirmed influenza A infection, and had positive viral titers at baseline. Both the peramivir and oseltamivir groups in each age cohort had approximately equal percentages of male and female subjects. The ITTI population from the 2 to <7 year-old cohort included 5 subjects between the age of 2 to <4 years (all in the peramivir group) and 24 subjects between the age of 4 to <7 years (88%, peramivir group; 13%, oseltamivir group). No meaningful differences were observed in the baseline influenza composite scores between treatment groups across age cohorts.

Table 7.2-2: Demographic and Baseline Charcteristics by Age & Treatment Group - Intent-to-Treat-Infected Population (Data Cutoff of March 2017)

	2 -<7 year-old cohort		7 -<13 year-old cohort		13 -<18 year-old cohort	
Baseline Characteristics	**Peramivir N=26**	**Oseltamivir N=3**	**Peramivir N=30**	**Oseltamivir N=7**	**Peramivir N=13**	**Oseltamivir N=5**
Sex, n (%)						
Male	15 (58%)	1 (33%)	15 (50%)	2 (29%)	8 (62%)	3 (60%)
Female	11 (42%)	2 (67%)	15 (50%)	5 (71%)	5 (38%)	2 (40%)
Age (years)						
Median (Q1–Q3)	5.1 (4.5–6.2)	4.1 (3.6–5.1)	8.7 (7.8–11.6)	9.2 (9.1–11.5)	15.6 (14.8–17.0)	16.7 (14.5–17.1)
Min, Max	2.3, 6.7	3.0, 6.1	7.2, 12.2	8.0, 12.9	13.7, 17.4	14.0, 17.7
Race, n (%)						
White	25 (96%)	3 (100%)	26 (87%)	7 (100%)	12 (92%)	5 (100%)
Black or African American	1 (4%)	0	4 (13%)	0	1 (8%)	0
Ethnicity						
Hispanic or Latino	7 (27%)	1 (33%)	8 (27%)	2 (29%)	3 (23%)	0
Not Hispanic/Latino	19 (73%)	2 (67%)	22 (73%)	5 (71%)	10 (77%)	5 (100%)
Weight (kg)						
Median (Q1–Q3)	19.1 (18.1–22.7)	14.1 (13.8–19.8)	34.0 (26.5–43.1)	36.8 (30.8–50.4)	76.9 (62.6–81.4)	59.9 (58.7–61.2)
Min, Max	13.6, 39.5	13.4, 25.4	21.3, 71.6	25.4, 71.2	54.4, 111.9	40.5, 62.1
Influenza type, n (%)						
A/H1N1	7 (27%)	2 (66%)	10 (33%)	3 (43%)	4 (31%)	4 (80%)
A/H3N2	9 (35%)	1 (33%)	7 (23%)	1 (14%)	2 (15%)	1 (20%)
A/Indeterminate	0	0	1 (3%)	0	0	0
B	6 (23%)	0	12 (40%)	3 (43%)	7 (54%)	0
A + B co-infection[a]	4 (15%)	0	0	0	0	0
Viral titer, n (%)						
Positive	22 (85%)	2 (67%)	27 (90%)	6 (86%)	12 (92%)	5 (100%)
Negative	4 (15%)	1 (33%)	3 (10%)	1 (14%)	1 (8%)	0
Composite Symptom Score						
N	21	2	21	5	12	5
Median (Q1–Q3)	10 (5–12)	10 (5–14)	14 (12–17)	15 (13–18)	13 (10–16)	12 (12–13)
Min, Max	3, 15	5, 14	5, 20	12, 19	7, 19	9, 21

[a] Influenza A + B co-infection included those with influenza A/H1N1 + B (n=1), influenza A/H3N2 + B (n=2), and influenza A/Indeterminate + B (n=1).
Source: Adapted from interim clinical study report and 90-day safety update for BCX1812-305, demographic data Listing 16.2.4.3-90d and Tables 14.1.2.1.3-90d, 14.1.4.2.4, and 14.1.4.2.5; Clinical reviewer's calculations.

7.3 Subject Disposition

Table 7.3-1 summarizes the subject disposition as of the data cutoff of March 2017. A total of 93 and 22 subjects were randomized to peramivir and oseltamivir treatment, respectively. Eighty-eight (95%) of the subjects randomized to peramivir and 22 (100%) of the subjects randomized to oseltamivir received at least one dose of study drug. The majority of subjects completed the study, including 94% of subjects in the peramivir group and 91% of subjects in the oseltamivir group. The most common reason for premature discontinuation from the study was withdrawal of consent prior to receiving study drug (5 [4%] subjects overall), all from the peramivir group. Three of the five subjects who withdrew consent in the peramivir group did so because of difficulty starting an IV or subject refusing to get stuck with a needle. Two subjects, one from each treatment group in the 7 to <13 year-old cohort, were lost to follow-up after receiving study drug. One of the subjects received peramivir and had confirmed influenza A/H3N2, while the other subject received oseltamivir and did not have confirmed influenza. There was one subject from the oseltamivir group (2 to <7 year-old cohort) who had confirmed influenza A/H1N1 and prematurely discontinued the study due to an adverse event (hallucinations) after receiving study drug. None of the subjects in the peramivir group discontinued the study due to an adverse event. Please see Section 8.3.3-1 for information regarding dropouts in Study BCX1812-305.

Table 7.3-1: Subject Disposition – Intent-to-Treat Population (Data cutoff of March 2017)

	Peramivir N=93 n (%)	**Oseltamivir N=22 n (%)**	**Total N=115 n (%)**
Completed Study	87 (94%)	20 (91%)	107 (93%)
Prematurely Discontinued Study	6 (6%)	2 (9%)	8 (7%)
Withdrawal of consent	5 (5%)	0	5 (4%)
Lost to follow-up	1 (1%)	1 (5%)	2 (2%)
Adverse event	0	1 (5%)	1 (1%)

Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Table 9; Clinical reviewer's calculations.

7.4 Analysis of Efficacy Endpoints

Efficacy outcomes were secondary endpoints for Study BCX1812-305. The results of the following key clinical efficacy endpoints are discussed below: time to alleviation of symptoms (TTAS), time to resolution of fever (TTRF), antipyretic usage, and incidence of influenza-related complications. Please see Section 6 and clinical virology review by William Ince, Ph.D. for discussion of the virologic endpoints in Study BCX1812-305.

Time to Alleviation of Influenza Symptoms

Table 7.4-1 summarizes the TTAS by age cohort. Overall, influenza symptoms were alleviated more rapidly in the peramivir group compared to the oseltamivir group (median 79.0 hours versus 107.4 hours). Among peramivir-treated subjects, median TTAS was not notably different for each age cohort. Most of the subjects included in the TTAS analysis were in the 7 to <13 year-old cohort, where median TTAS was shorter in the peramivir group compared to

the oseltamivir group (63.9 hours versus 133.6 hours). The peramivir groups in the other age cohorts had a longer median TTAS compared to the oseltamivir groups. Results of these subgroup analyses cannot be reliably interpreted due to limited evidence, as the oseltamivir group had only two subjects in the 2 to <7 year-old cohort and only five subjects in the 13 to <18 year-old cohort.

Table 7.4-1: Time to Alleviation of Symptoms (Kaplan-Meier Estimate [hours]) by Age Cohort - Intent-to-Treat Infected Population (Data cutoff of March 2017)

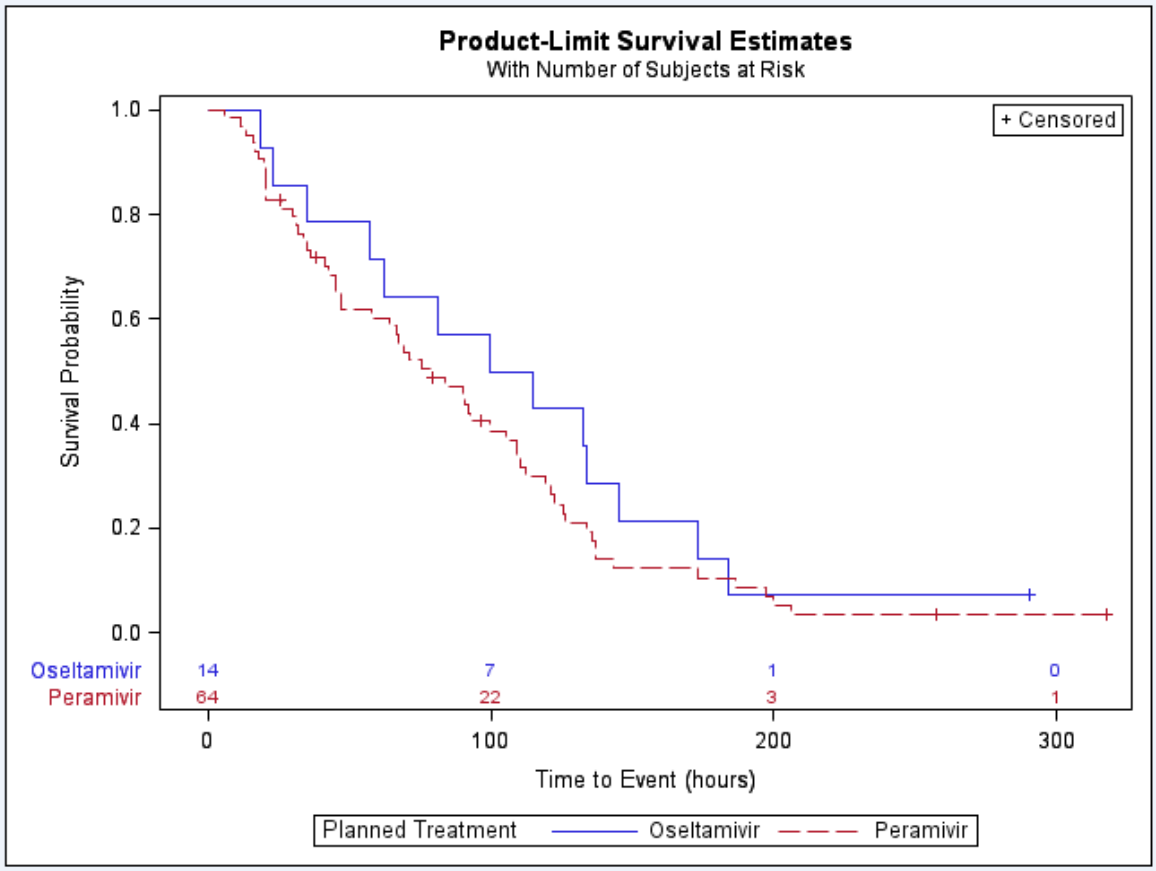
Age Group	Peramivir	Oseltamivir	Total
Overall			
N (number censored)	64 (6)	14 (1)	78 (7)
Median (Q1, Q3)	79.0 (34.0, 122.4)	107.4 (57.3, 145.3)	83.7 (34.9, 132.5)
Mean	85.7	103.1	89.2
Min – Max	5.6 – 317.6	18.4 – 290.6	5.6 – 317.6
Age 2 to <7 years			
N (number censored)	23 (1)	2 (0)	25 (1)
Median (Q1, Q3)	99.9 (34.0, 135.8)	20.7 (18.4, 23.1)	90.7 (30.9, 135.8)
Mean	92.7	20.7	87.0
Min – Max	13.2 – 205.8	18.4 – 23.1	13.2 – 205.8
Age 7 to <13 years			
N (number censored)	28 (4)	7 (0)	35 (4)
Median (Q1, Q3)	63.9 (25.9, 109.2)	133.6 (114.9, 173.3)	75.6 (34.9, 126.4)
Mean	66.6	134.4	84.6
Min – Max	5.6 – 317.6	57.3 – 183.9	5.6 – 317.6
Age 13 to <18 years			
N (number censored)	13 (1)	5 (1)	18 (2)
Median (Q1, Q3)	92.1 (45.1, 172.8)	81.0 (62.3, 99.8)	86.6 (45.1, 172.8)
Mean	101.3	75.5	99.5
Min – Max	11.6 – 199.5	34.7 – 290.6	11.6 – 290.6

Note: Six subjects were excluded from summaries due to missing data or events resolving prior to initiation of study drug. Subjects at risk were the number at risk at the beginning of the interval. Cumulative events and Kaplan-Meier % were at the end of the interval.

Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Table 28; Clinical and Statistical reviewer's calculations.

Kaplan-Meier plots of time to alleviation of symptoms for the overall ITTI population show earlier declines in the peramivir treatment group compared to oseltamivir (Figure 7.4-1). However, the difference between treatment groups was not statistically significant (Wilcoxon p-value=0.29).

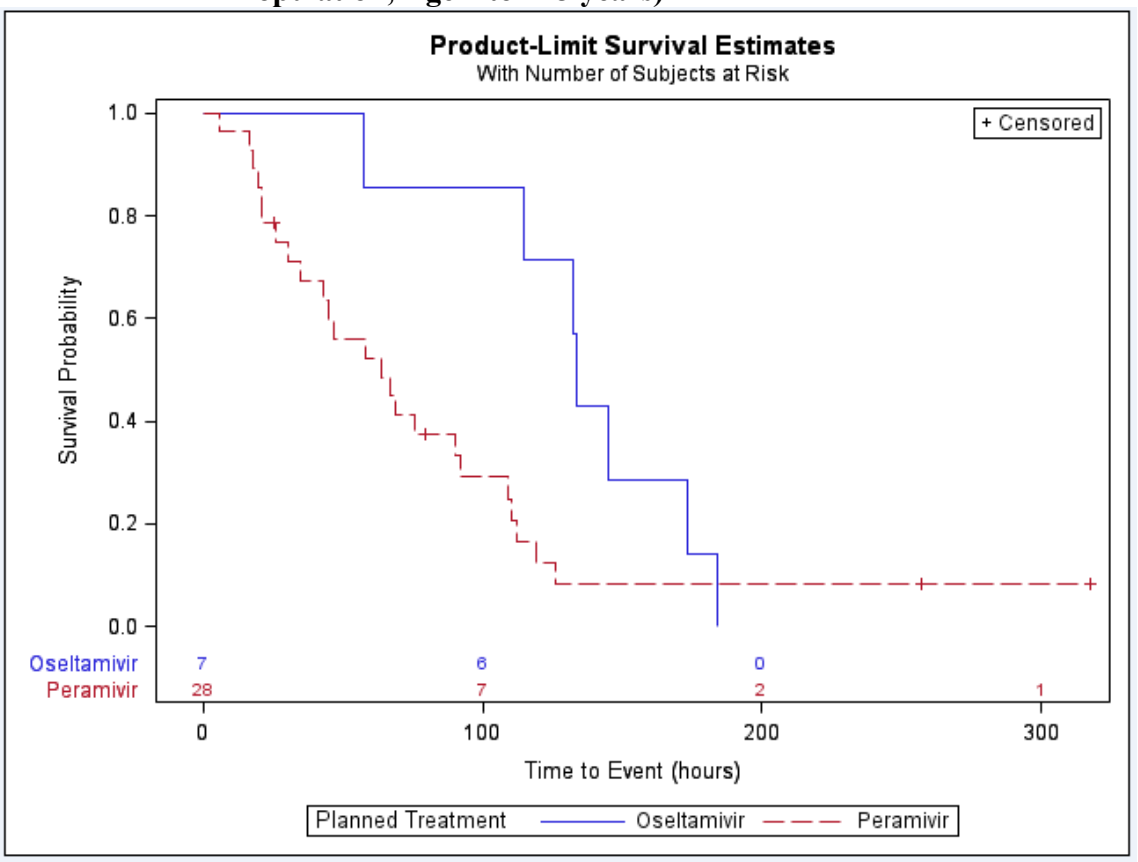
Figure 7.4-1: Kaplan-Meier Plot of Time to Alleviation of Symptoms (ITT-Infected Population, Age 2 to <18 years)



Source: Statistical Reviewer's analysis.

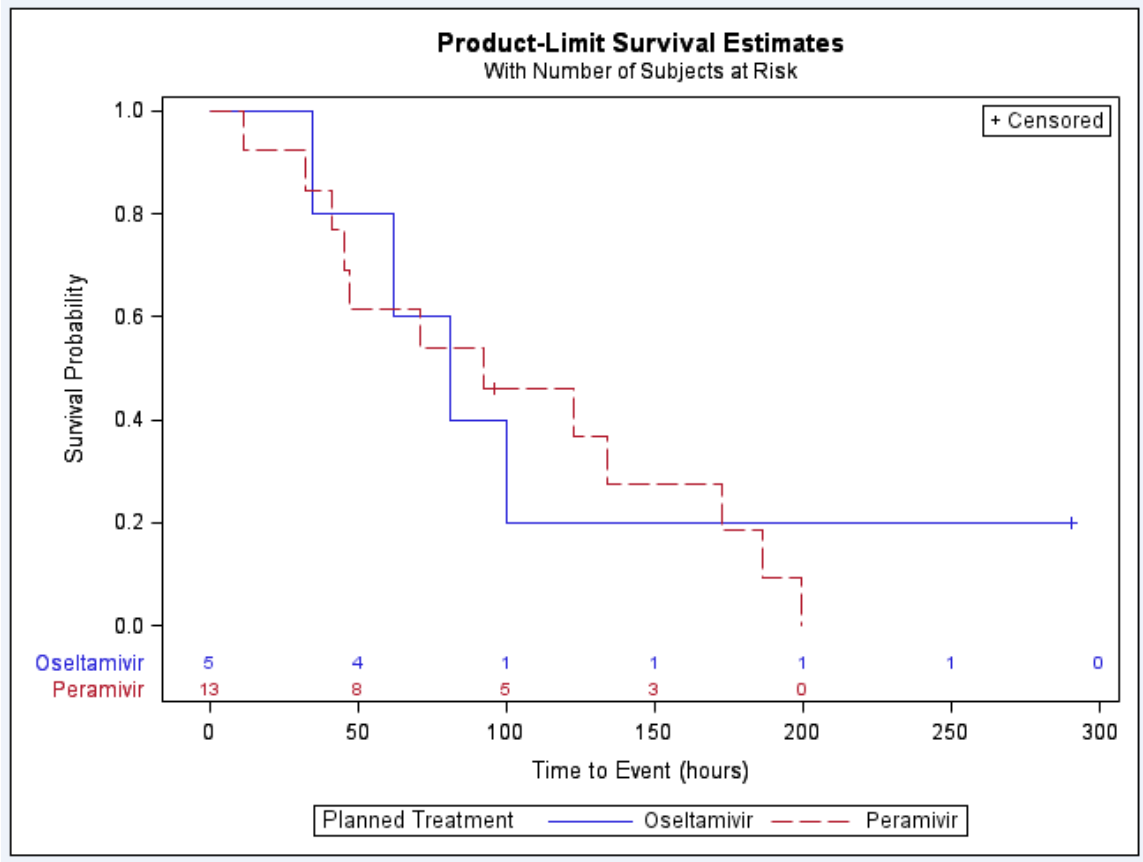
Kaplan-Meier plots of time to alleviation of symptoms only show earlier declines in the peramivir treatment group (compared with oseltamivir) in the 7 to <13 year-old cohort (Figure 7.4-2). There appeared to be no treatment group difference in rates of decline in the 13 to <18 year old cohort (Figure 7.4-3). There were only two oseltamivir subjects in the 2 to <7 year-old cohort, so the plot for this age group is not shown.

Figure 7.4-2: Kaplan-Meier Plot of Time to Alleviation of Symptoms (ITT-Infected Population, Age 7 to <13 years)



Source: Statistical Reviewer's analysis.

Figure 7.4-3: Kaplan-Meier Plot of Time to Alleviation of Symptoms (ITT-Infected Population, Age 13 to <18 years)



Source: Statistical Reviewer's analysis.

Time to Resolution of Fever

Table 7.4-2 summarizes the time to resolution of fever by age cohort. Overall, fever took longer to resolve in the peramivir group compared with the oseltamivir group (median 40.0 hours versus 28.3 hours, respectively). Among subjects who received peramivir, the median TTRF was not notably different for each age cohort. Most of the subjects included in the TTRF analysis were in the 7 to <13 year-old cohort, where median TTRF was shorter in the peramivir group compared to the oseltamivir group (31.3 hours versus 38.3 hours, respectively). The peramivir groups in the other age cohorts had a longer median TTRF compared to the oseltamivir groups. Based on the small sample sizes, however, these subgroup findings should be interpreted with caution.

Table 7.4-2: Time to Resolution of Fever (Kaplan-Meier Estimate [hours]) by Age Cohort - Intent-to-Treat Infected Population (Data cutoff of March 2017)

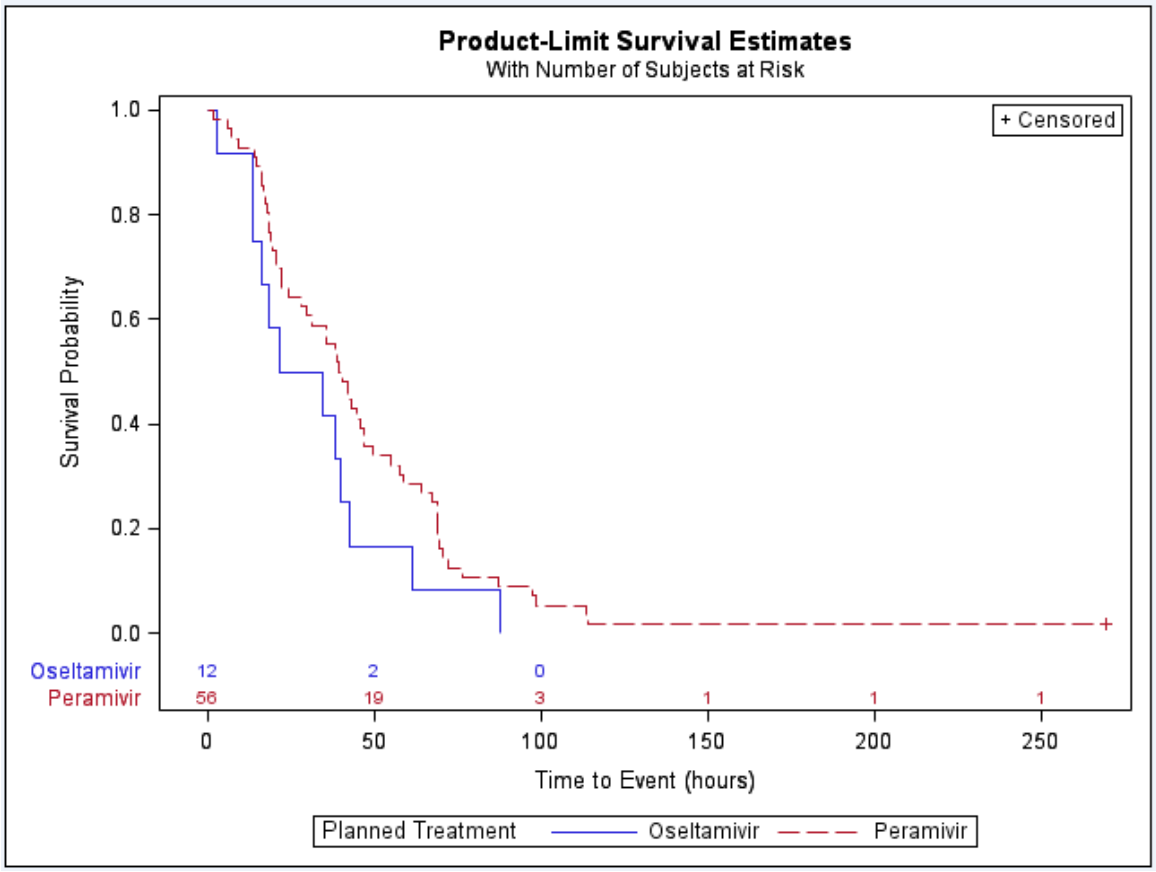
Age Group	Peramivir	Oseltamivir	Total
Overall			
N (number censored)	56 (1)	12 (0)	68 (1)
Median (Q1, Q3)	40.0 (19.2, 68.2)	28.3 (14.8, 41.0)	38.6 (18.5, 62.8)
Mean	44.5	32.6	42.4
Min - Max	1.5 – 269.6	2.9 – 87.8	1.5 – 269.6
Age 2 to <7 years			
N (number censored)	20 (1)	2 (0)	22 (1)
Median (Q1, Q3)	43.1 (29.0, 70.5)	16.0 (13.7, 18.4)	39.2 (24.4, 69.0)
Mean	51.8	16.0	48.6
Min - Max	17.1 – 269.6	13.7 - 18.4	13.7 – 269.6
Age 7 to <13 years			
N (number censored)	27 (0)	5 (0)	32 (0)
Median (Q1, Q3)	31.3 (17.9, 47.0)	38.3 (16.0, 39.8)	33.5 (17.2, 45.4)
Mean	36.3	27.9	35.0
Min - Max	1.5 – 113.4	2.9 – 42.3	1.5 – 113.4
Age 13 to <18 years			
N (number censored)	9 (0)	5 (0)	14 (0)
Median (Q1, Q3)	58.8 (16.0, 69.5)	34.7 (21.8, 61.6)	50.3 (16.0, 69.5)
Mean	51.3	43.9	48.6
Min - Max	5.8 – 114.1	13.4 – 87.8	5.8 – 114.1

Note: Sixteen subjects were excluded from summaries due to missing data or events resolving prior to initiation of study drug. Subjects at risk were the number at risk at the beginning of the interval. Cumulative events and Kaplan-Meier % were at the end of the interval.

Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Table 30; Clinical and Statistical reviewer's calculations.

Kaplan-Meier plots of time to resolution of fever for the overall ITTI population show earlier declines in the oseltamivir treatment group compared with peramivir (Figure 7.4-4). However, the difference between treatment groups was not statistically significant (Wilcoxon p-value=0.11).

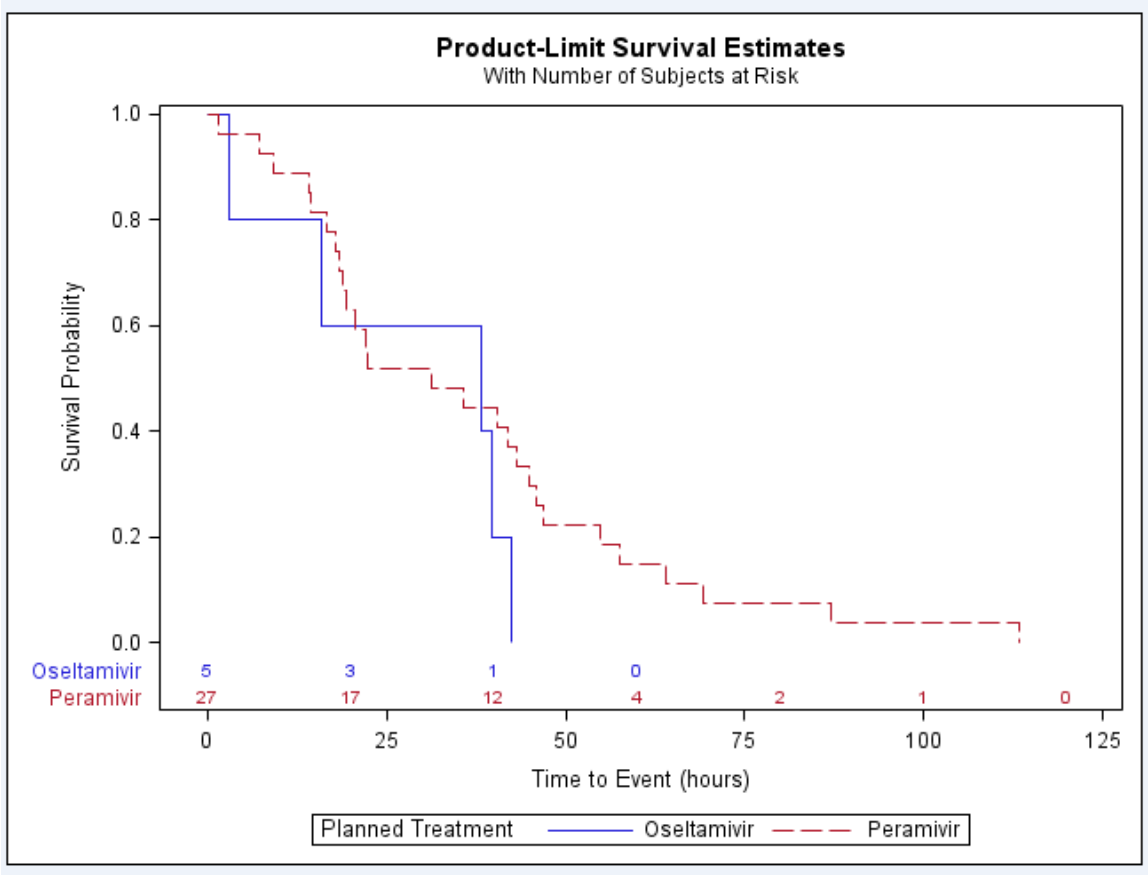
Figure 7.4-4: Kaplan-Meier Plot of Time to Resolution of Fever (ITT-Infected Population, Age 2 to <18 years)



Source: Statistical Reviewer's analysis.

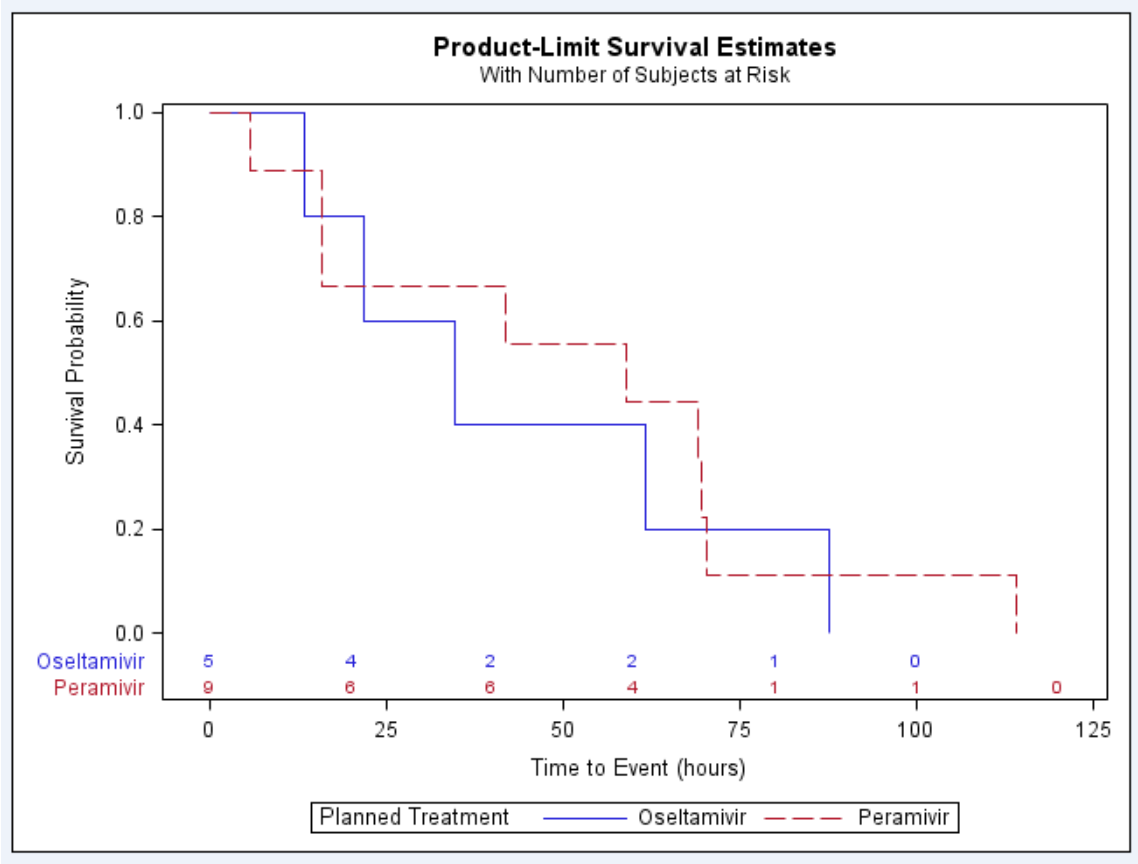
Kaplan-Meier plots of time to resolution of fever show earlier declines in the oseltamivir treatment group (compared with peramivir) in the 2 to <7 year-old and 13 to <18 year-old cohorts. However, there were only two oseltamivir subjects in the 2 to <7 year old subgroup so the Kaplan-Meier plot for this age group is not shown.

Figure 7.4-5: Kaplan-Meier Plot of Time to Resolution of Fever (ITT-Infected Population, Age 7 to <13 years)



Source: Statistical Reviewer's analysis.

Figure 7.4-6: Kaplan-Meier Plot of Time to Resolution of Fever (ITT-Infected Population, Age 13 to <18 years)



Source: Statistical Reviewer's analysis.

Antipyretic Usage

Use of antipyretic medications was allowed during Study BCX1812-305 and included any product containing acetaminophen or ibuprofen. The majority of subjects in the ITTI population reported antipyretic use during the study, including 58 subjects (84%) in the peramivir group and 14 subjects (93%) in the oseltamivir group. All subjects in the Kaplan-Meier plots of TTAS and TTRF (including censored subjects) were evaluated more closely by the clinical reviewer because the treatment benefit of peramivir over oseltamivir on TTAS or of oseltamivir over peramivir on TTRF may have been confounded by concomitant antipyretic use.

As shown in Table 7.4-3, antipyretic use was reported in the majority of subjects included in the Kaplan-Meier plot of TTAS (86% peramivir group, 100% oseltamivir group). The median number of doses and days of antipyretic use were also similar in each treatment group. No meaningful differences were observed across the age cohorts with regards to antipyretic use among subjects included in the TTAS analysis.

Table 7.4-3: Antipyretic Use in the TTAS analysis - Intent-to-Treat Infected Population (Data cutoff of March 2017)

Age Group	Peramivir	Oseltamivir	Total
Overall			
Total N	64	14	78
Any antipyretic usage, n (%)	55 (86%)	14 (100%)	69 (88%)
No. of doses administered, median (min – max)	3 (1 – 20)	4 (1 – 13)	3 (1 – 20)
No. of days administered, median (min – max)	2 (1 – 7)	3 (1 – 8)	2 (1 – 8)
Age 2 to <7 years			
Total N	23	2	25
Any antipyretic usage, n (%)	21 (91%)	2 (100%)	23 (92%)
No. of doses administered, median (min – max)	3 (1 – 10)	4 (1 – 7)	3 (1 – 10)
No. of days administered, median (min – max)	2 (1 – 4)	2 (1 – 3)	2 (1 – 4)
Age 7 to <13 years			
Total N	28	7	35
Any antipyretic usage, n (%)	25 (89%)	7 (100%)	32 (91%)
No. of doses administered, median (min – max)	3 (1 – 16)	2 (1 – 9)	2 (1 – 16)
No. of days administered, median (min – max)	2 (1 – 5)	2 (1 – 4)	2 (1 – 5)
Age 13 to <18 years			
Total N	13	5	18
Any antipyretic usage, n (%)	9 (69%)	5 (100%)	14 (78%)
No. of doses administered, median (min – max)	3 (1 – 20)	5 (4 – 13)	5 (1 – 20)
No. of days administered, median (min – max)	3 (1 – 7)	4 (3 – 8)	3 (1 – 8)

Source: Clinical and Statistical reviewer's calculations.

As shown in Table 7.4-4, antipyretic use was reported in the majority of subjects included in the Kaplan-Meier plot of TTRF (89% peramivir group, 100% oseltamivir group). The median number of doses and days of antipyretic use were also similar in the peramivir and oseltamivir groups. No meaningful differences were observed across the age cohorts with regards to antipyretic use among subjects included in the TTRF analysis.

Table 7.4-4: Antipyretic Use in the TTRF analysis - Intent-to-Treat Infected Population (Data cutoff of March 2017)

Age Group	Peramivir	Oseltamivir	Total
Overall			
Total N	56	12	68
Any antipyretic usage, n (%)	50 (89%)	12 (100%)	62 (91%)
No. of doses administered, median (min – max)	3 (1 – 20)	5 (1 – 13)	4 (1- 20)
No. of days administered, median (min – max)	2 (1 – 7)	3 (1 – 8)	2 (1 – 8)
Age 2 to <7 years			
Total N	20	2	22
Any antipyretic usage, n (%)	19 (95%)	2 (100%)	21 (95%)
No. of doses administered, median (min – max)	4 (1 – 10)	4 (1 – 7)	4 (1 – 10)
No. of days administered, median (min – max)	2 (1 – 4)	2 (1 – 3)	2 (1 – 4)
Age 7 to <13 years			
Total N	27	5	32
Any antipyretic usage, n (%)	23 (85%)	5 (100%)	28 (88%)
No. of doses administered, median (min – max)	3 (1 – 16)	2 (1 – 9)	3 (1 – 16)
No. of days administered, median (min – max)	2 (1 – 5)	2 (1 – 4)	2 (1 – 5)
Age 13 to <18 years			
Total N	9	5	14
Any antipyretic usage, n (%)	8 (89%)	5 (100%)	13 (93%)
No. of doses administered, median (min – max)	4 (1 – 20)	5 (4 – 13)	5 (1 – 20)
No. of days administered, median (min – max)	3 (1 – 7)	4 (3 – 8)	3 (1 – 8)

Source: Clinical and Statistical reviewer's calculations.

The majority of subjects in both treatment groups started using antipyretic medications at the beginning of the trial. There was no statistically significant difference between time to antipyretic medication use in the two treatment groups (Wilcoxon p-value=0.90). The ability to delineate the effect of antipyretics on outcome is limited by the study design, where the use of antipyretics was not a baseline randomization factor and the majority of patients received antipyretics post-baseline. Nevertheless, no imbalance in antipyretic usage was observed between treatment groups.

Influenza-Related Complications

There were four subjects (6%) in the peramivir group, including three in the 2 to <7 year-old cohort and one in the 7 to <13 year-old cohort, who had one or more influenza-related complications (diagnosed by physical exam), compared with zero subjects in the oseltamivir group. The influenza-related complication reported in the 7 to <13 year-old cohort was otitis media on Day 7 (Subject 009.004, influenza B infection). The influenza-related complications reported in the 2 to <7 year-old cohort were:

- Sinusitis diagnosed on Day 1 (Subject 005.035, influenza A/H3N2 + B co-infection)
- Sinusitis and otitis media diagnosed on Day 1 (Subject 005.036, influenza A/H3N2 infection)
- Otitis media diagnosed on Day 14 (Subject 008.019, influenza A/H3N2 infection).

All of the reported investigator-diagnosed conditions resolved within 1 or 2 weeks. No other influenza-related complications besides these three cases of otitis media and two cases of sinusitis were reported during the trial. Although the incidence of influenza-related complications was higher in the peramivir group compared with the oseltamivir group, the small number of events limits interpretation.

7.5 Subpopulations

Subgroup analysis of the key clinical efficacy endpoints were conducted for each treatment arm. Based on the small sample sizes, no meaningful differences could be observed across the following relevant subgroups: sex, race, and ethnicity. Please see Section 7.4 (Tables 7.4-1 and 7.4-2) for analysis of TTAS and TTRF by age cohort. Analysis of TTAS and TTRF by influenza virus subtype are discussed below. Based on the small sample sizes and multiple subgroup analyses, these results should be interpreted with caution.

Influenza Subtype

Table 7.5-1 summarizes the time to alleviation of symptoms by influenza virus subtype (influenza A/H1N1, influenza A/H3N2, and influenza B). Among subjects who received peramivir, the median TTAS was not notably different for each influenza virus subtype. Influenza symptoms were alleviated more rapidly in the peramivir group compared with the oseltamivir group for influenza A/H1N1 (median 75.6 hours versus 116.7 hours, respectively) and influenza B (median 70.8 hours versus 114.9 hours, respectively). In contrast, the median TTAS was slightly longer in the peramivir group compared with the oseltamivir group for influenza A/H3N2 (83.7 hours versus 81.0 hours, respectively). Results of these subgroup analyses cannot be reliably interpreted due to limited evidence, as the oseltamivir group had only three subjects with influenza A/H3N2 and only three subjects with influenza B.

Table 7.5-1: Time to Alleviation of Symptoms (Kaplan-Meier Estimate [hours]) by Influenza Subtype - Intent-to-Treat Infected Population (Data cutoff of March 2017)

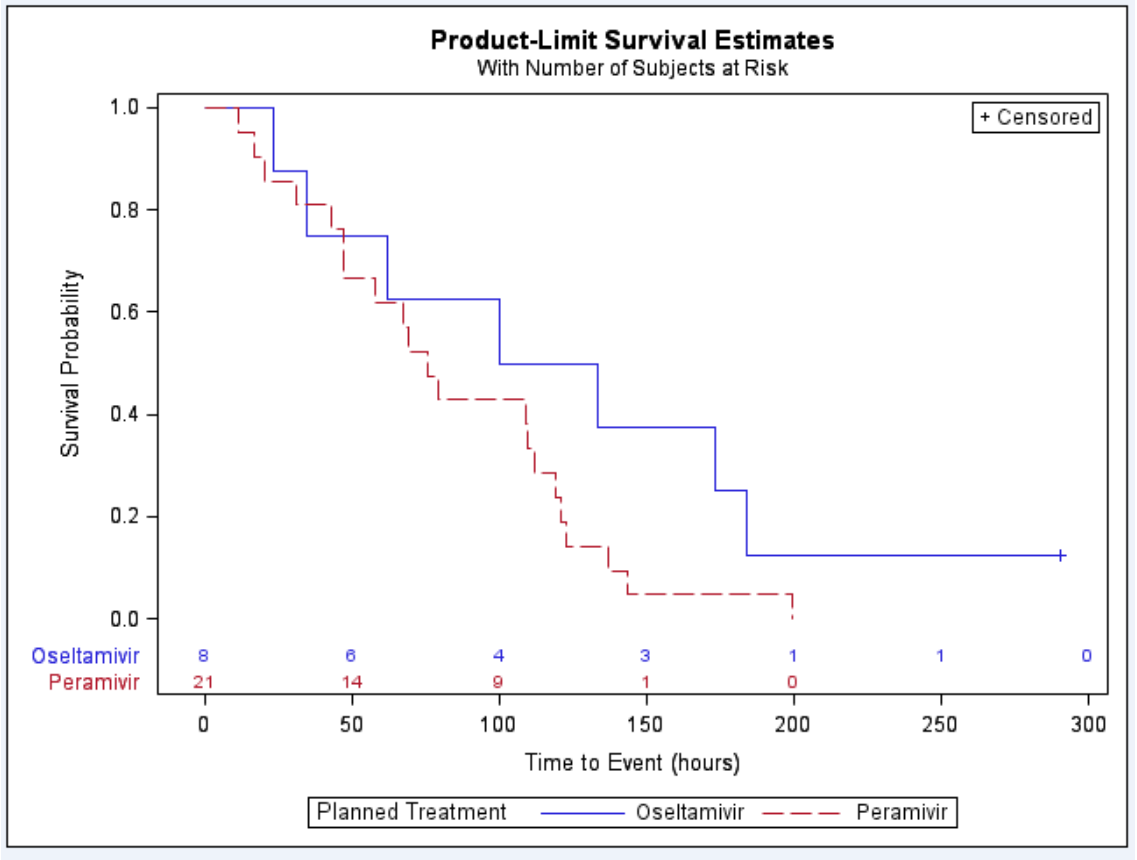
Influenza Subtype	Peramivir	Oseltamivir	Total
A/H1N1			
N (number censored)	21 (0)	8 (1)	29 (1)
Median (Q1, Q3)	75.6 (47.0, 118.9)	116.7 (48.5, 178.6)	79.0 (47.0, 122.4)
Mean	82.8	111.8	91.3
Min - Max	11.6 – 199.5	23.1 – 290.6	11.6 – 290.6
A/H3N2			
N (number censored)	15 (3)	3 (0)	18 (3)
Median (Q1, Q3)	83.7 (25.9, 99.9)	81.0 (18.4, 132.5)	83.7 (25.9, 125.7)
Mean	82.2	77.3	81.4
Min - Max	13.2 – 317.6	18.4 – 132.5	13.2 – 317.6
B			
N (number censored)	23 (3)	3 (0)	26 (3)
Median (Q1, Q3)	70.8 (34.0, 133.7)	114.9 (57.3, 145.3)	81.5 (34.9, 133.7)
Mean	91.2	105.8	92.4
Min - Max	5.6 – 257.2	57.3 – 145.3	5.6 – 257.2

Note: Six subjects were excluded from summaries due to missing data or events resolving prior to initiation of study drug. Subjects who did not experience alleviation of symptoms were censored at the last observed symptom assessment.

Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Table 28A; Clinical and Statistical reviewer's calculations.

Kaplan-Meier plots of time to alleviation of symptoms show earlier declines in the peramivir treatment group (compared with oseltamivir) for influenza A/H1N1 (Figure 7.5-1). There were only three oseltamivir subjects with influenza A/H3N2 and B subtypes each, so the Kaplan-Meier plots for those subtypes are not shown.

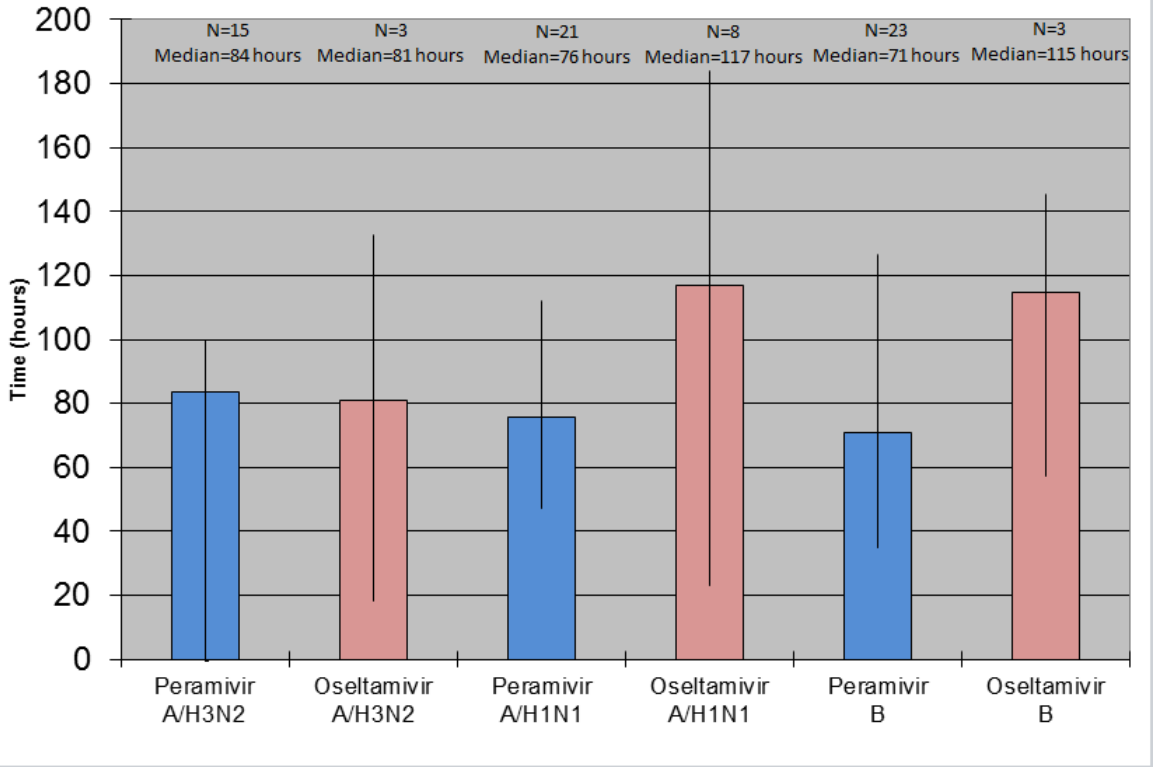
Figure 7.5-1: Kaplan-Meier Plot of Time to Alleviation of Symptoms, Influenza Subtype A/H1N1 (ITT-Infected Population, Age 2 to <18 years)



Source: Statistical Reviewer's analysis.

In Figure 7.5-2, Kaplan-Meier estimates of the median time to alleviation of symptoms of influenza by viral subtype and the 95% CI of the median are plotted by treatment group. As evident from the plot, the 95% CIs for the peramivir and oseltamivir groups overlap, indicating no statistically significance difference between the medians of the two treatment groups.

Figure 7.5-2: Median (95% CI) Time to Alleviation of Symptoms by Viral Subtype – Intent-to-Treat Infected Population (Age 2 to <18 years)



Source: Statistical Reviewer's analysis.

Table 7.5-2 summarizes the time to resolution of fever for the relevant influenza virus subtypes (influenza A/H1N1, influenza A/H3N2, and influenza B). Among subjects who received peramivir, the median TTRF was not notably different for each influenza subtype. Fever resolved more rapidly in the peramivir group compared to the oseltamivir group for influenza B (median 31.4 hours versus 39.0 hours, respectively), but there were only two oseltamivir-treated subjects in this subgroup. Median TTRF was longer in the peramivir group compared with the oseltamivir group for influenza A/H1N1 (47.0 hours versus 34.7 hours, respectively) and influenza A/H3N2 (39.2 hours versus 18.4 hours, respectively). Based on the small sample sizes and multiple subgroup analyses, however, these results should be interpreted with caution.

Table 7.5-2: Time to Resolution of Fever (Kaplan-Meier Estimate [hours]) by Influenza Subtype - Intent-to-Treat Infected Population (Data cutoff of March 2017)

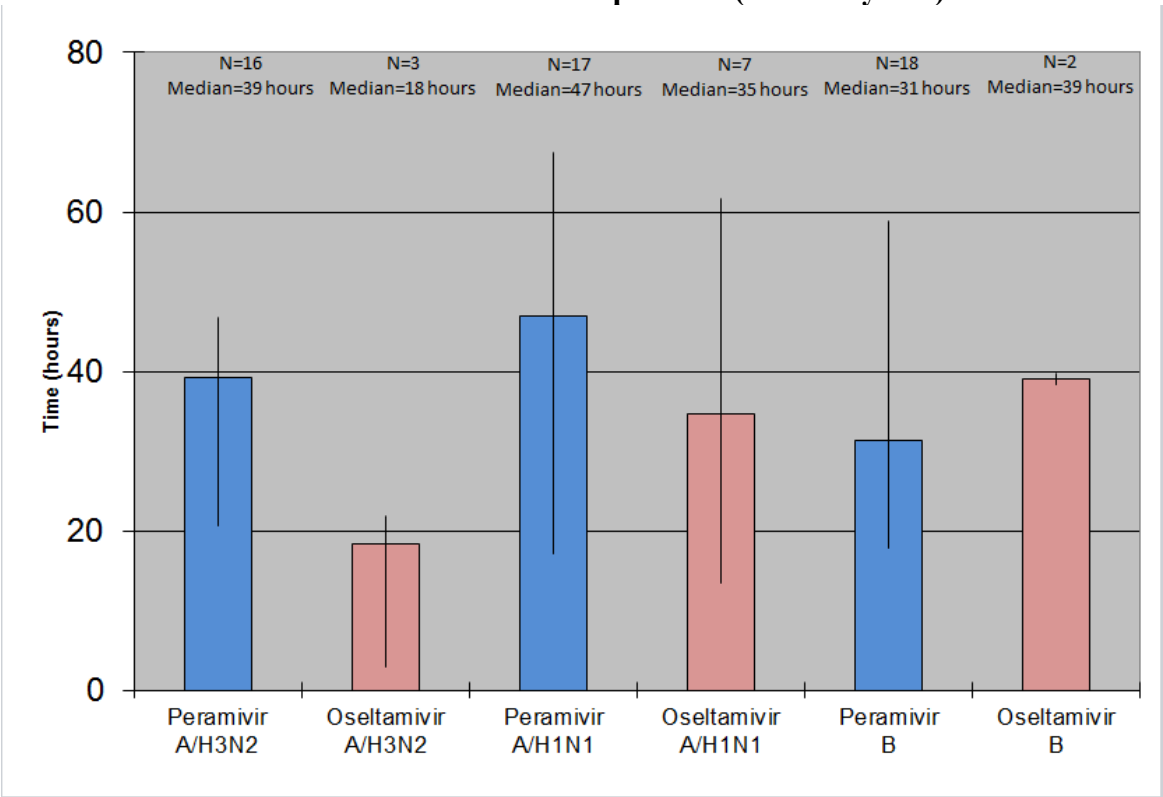
Influenza Subtype	Peramivir	Oseltamivir	Total
A/H1N1			
N (number censored)	17 (0)	7 (0)	24 (0)
Median (Q1, Q3)	47.0 (31.3, 67.5)	34.7 (13.7, 61.6)	43.6 (16.8, 65.7)
Mean	47.0	38.5	44.5
Min - Max	14.5 – 87.0	13.4 – 87.8	13.4 – 87.8
A/H3N2			
N (number censored)	16 (1)	3 (0)	19 (1)
Median (Q1, Q3)	39.2 (22.6, 57.9)	18.4 (2.9, 21.8)	38.4 (18.9, 46.8)
Mean	46.3	14.4	41.2
Min - Max	1.5 – 269.6	2.9 – 21.8	1.5 – 269.6
B			
N (number censored)	18 (0)	2 (0)	20 (0)
Median (Q1, Q3)	31.4 (17.9, 69.0)	39.0 (38.3, 39.8)	39.0 (18.2, 63.9)
Mean	42.1	39.0	41.8
Min - Max	5.8 – 113.4	38.3 – 39.8	5.8 – 113.4

Note: Sixteen subjects were excluded from summaries due to missing data or events resolving prior to initiation of study drug. Subjects who did not experience resolution of fever were censored at the time of their last non-missing temperature assessment.

Source: Adapted from updated clinical study report tables/figures for Study BCX1812-305, Table 30A; Clinical and Statistical reviewer's calculations.

In Figure 7.5-3, Kaplan-Meier estimates of the median time to resolution of fever by viral subtype and the 95% CI of the median are plotted by treatment group, and appear to show the greatest treatment difference between medians occurred in the influenza A/H3N2 subgroup.

Figure 7.5-3: Median (95% CI) Time to Resolution of Fever by Viral Subtype – Intent-to-Treat Infected Population (2 to <18 years)



Source: Statistical Reviewer's analysis.

Duration of Influenza Symptoms

When the duration of influenza symptoms prior to treatment was taken into account, Kaplan-Meier plots of the overall ITTI population showed slightly earlier declines in TTAS for subjects with duration of illness exceeding 24 hours (compared with subjects treated within the first 24 hours). However, this difference was not statistically significant (Wilcoxon p-value=0.33).

Table 7.5-3 summarizes the TTAS by duration of illness prior to treatment (0 to 24 hours, >24 hours). Influenza symptoms were alleviated more rapidly in the peramivir group compared with the oseltamivir group for subjects treated within 24 hours of influenza symptom onset (median 76 hours versus 133 hours, respectively). In contrast, TTAS was similar between the two treatment groups among subjects treated more than 24 hours after symptom onset.

Table 7.5-3: Time to Alleviation of Symptoms (Kaplan-Meier Estimate [hours]) by Duration of Illness - Intent-to-Treat Infected Population (Data cutoff of March 2017)

Duration of Illness	Peramivir	Oseltamivir	Total
0 to ≤ 24 hours			
N (number censored)	33 (4)	6 (1)	39 (5)
Median (Q1, Q3)	76 (47, 122)	133 (100, 173)	90 (43, 134)
Mean	88	122	95
Min - Max	18 - 318	18 - 291	18 - 318
>24 hours			
N (number censored)	31 (2)	8 (0)	39 (2)
Median (Q1, Q3)	84 (21, 126)	72 (46, 130)	81 (26, 126)
Mean	82	88	83
Min - Max	6 - 257	23 - 184	6 - 257

Source: Statistical Reviewer's analysis.

7.6 Additional Efficacy Issues/Analyses

Overall, a favorable clinical effect was observed in both treatment groups for the Subject Diary assessments of usual daily activities and appetite/eating patterns. The median ability to perform daily activities assessment was at the maximum value (10) by Day 8 and Day 9 in the peramivir and oseltamivir groups, respectively. All subjects in the peramivir and oseltamivir groups had appetite/eating patterns improved from abnormal or reduced to normal by Day 14.

8. Safety

Safety Summary

Safety data from 88 peramivir-treated subjects in Study BCX1812-305 support the safety of peramivir in pediatric patients ≥2 years old. The safety profile of peramivir in children 2 to <18 years old was generally similar to that observed in adults. The majority of treatment emergent adverse events in Study BCX1812-305 were mild or moderate in severity and self-limited. There were no deaths, serious adverse events, or adverse events leading to withdrawal.

There were also no notable differences across the age cohorts with respect to safety. No new or unexpected toxicities were observed for IV peramivir in pediatric patients ≥2 years old.

8.1 Approach to the Safety Review

The pivotal safety data reviewed in this submission came from a single trial, BCX1812-305. As described in Section 7.1, Study BCX1812-305 is an ongoing Phase 3, multi-center, open-label, randomized, active-controlled trial being conducted in the U.S. The safety population includes all subjects who received at least one dose of peramivir (n=88) or oseltamivir (n=22). Safety data were analyzed by the clinical reviewer using JReview software.

The primary endpoints of Study BCX1812-305 were the safety assessments of Adverse Events (AEs), clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) and vital signs measurements. Treatment-emergent adverse events (TEAEs) were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 preferred terms and system organ class. Laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) were graded according to the Division of Acquired Immune Deficiency Syndrome (DAIDS) Table for Grading Adverse Events for Adults and Pediatrics (Publish Date: December 2004 Clarification 2009). Laboratory results considered clinically significant by the investigator were reported as AEs. Influenza-related complications were not considered AEs unless they met the criteria for a serious adverse event (SAE). Descriptive statistical methods were used to summarize the safety data. Although the trial included an active comparator arm, the sample sizes were not based on statistical considerations for detecting significant differences.

The original NDA submission for Rapivab® also included supportive safety information from a Phase 3, non-controlled, open-label study of IV peramivir in Japanese pediatric subjects (Shionogi Study 0918T0633). Children ≥28 days to <16 years of age with acute uncomplicated influenza were treated with IV peramivir 10 mg/kg for up to 5 days. Peramivir IV was noted to be generally safe and well tolerated; however, the peramivir dose in Study 0918T0633 was lower than that proposed for children ≥2 years old in this supplemental NDA. Please see the clinical review by Dr. Peter Miele in the original NDA for the results from Shionogi Study 0918T0633. The current review will focus on data from the pivotal trial, Study BCX1812-305.

8.2 Adequacy of Safety Assessments

8.2.1 Overall Exposure at Appropriate Doses/Duration and Demographics of Target Populations

This submission contains all the available safety data from 110 subjects age 2 to <18 years who enrolled and received study drug during Study BCX1812-305 (data cutoff March 2017). Eighty-eight subjects (80%) were treated with peramivir and all received a single 12 mg/kg dose (maximum 600 mg). One peramivir-treated subject prematurely discontinued the study and the reason was lost to follow-up on Day 3. There were 22 subjects (20%) who were treated with oseltamivir and all but two subjects received twice daily doses for 5 to 6 days (10 doses total). Two oseltamivir-treated subjects prematurely discontinued the study after a single dose, and the reasons for early withdrawal were adverse event (hallucinations) or lost to follow-up.

Table 8.2.1-1 summarizes the demographic characteristics of the 110 subjects in the Safety population. The peramivir group consisted of 46 males (52%) and 42 females (48%). There were 9 males (41%) and 13 females (59%) in the oseltamivir group. The median ages were 8.6 years (range 2.3 to 17.5 years) and 9.2 years (range 2.9 to 17.7 years) for the peramivir and oseltamivir groups, respectively. In the peramivir group, 32%, 44%, and 24% of subjects were in the 2 to <7 year-old, 7 to <13 year-old, and 13 to <18 year-old cohorts, respectively. In the oseltamivir group, 27%, 41%, and 32% of subjects were in the 2 to <7 year-old, 7 to <13 year-old, and 13 to <18 year-old cohorts, respectively. Over 90% of subjects in either treatment group were white. The maximum IV peramivir dose of 600 mg was administered to 32% of subjects treated with peramivir, including all 21 subjects in the 13 to <18 year-old cohort and 7 subjects in the 7 to <13 year-old cohort. The majority of subjects in both treatment groups had confirmed influenza by RT-PCR (78%, peramivir group; 68% oseltamivir group) and positive viral titers.

Table 8.2.1-1: Demographic by Treatment Group - Safety Population (Data Cutoff of March 2017)

Baseline Characteristics	Peramivir N=88	Oseltamivir N=22	Total N=110
Sex			
Male	46 (52%)	9 (41%)	55 (50%)
Female	42 (48%)	13 (59%)	55 (50%)
Age (years)			
Median (Q1–Q3)	8.6 (6.2–12.1)	9.2 (6.6–14.5)	8.8 (6.3–13.1)
Min, Max	2.3, 17.5	2.9, 17.7	2.3, 17.7
Age Group, n (%)			
2 - <7 years-old	28 (32%)	6 (27%)	34 (31%)
7 - <13 years-old	39 (44%)	9 (41%)	48 (44%)
13 - <18 years-old	21 (24%)	7 (32%)	28 (25%)
Race			
White	81 (92%)	22 (100%)	103 (94%)
Black or African American	6 (7%)	0	6 (5%)
Other	1 (1%)	0	1 (1%)
Ethnicity			
Hispanic or Latino	22 (25%)	5 (23%)	27 (25%)
Not Hispanic/Latino	66 (75%)	17 (77%)	83 (75%)
Weight (kg)			
Median (Q1–Q3)	33.0 (21.5–55.4)	36.9 (25.4–59.9)	33.9 (21.6–56.3)
Min, Max	13.6, 111.9	13.4, 71.2	13.4, 111.9
Confirmed Influenza by RT-PCR			
Positive	69 (78%)	15 (68%)	84 (76%)
Negative	19 (22%)	7 (32%)	26 (24%)
Influenza type, n (%)			
A/H1N1	21 (24%)	9 (41%)	30 (27%)
A/H3N2	18 (20%)	3 (14%)	21 (19%)
A/Indeterminate	1 (1%)	0	1 (1%)
B	25 (28%)	3 (14%)	28 (25%)
A + B co-infection[a]	4 (5%)	0	4 (4%)
Viral titer, n (%)			
Positive	61 (69%)	13 (59%)	74 (67%)

Negative	27 (31%)	9 (41%)	36 (33%)

[a] Influenza A + B co-infection included subjects with influenza A/H1N1 + B (n=1), influenza A/H3N2 + B (n=2), and influenza A/Indeterminate + B (n=1).

Source: Adapted from interim clinical study report and 90-Day safety update report for Study BCX1812-305, Tables 14.1.4.3.3-90d, and 14.1.4.3.4, and 14.1.4.3.5; Clinical reviewer's calculations.

Demographics and Baseline Characteristics by Age Cohort

Table 8.2.1-2 summarizes the demographic characteristics for Safety population by age cohort. As with the overall Safety population, most subjects in each age cohort were white and had confirmed influenza infection with positive viral titers at baseline. Both the peramivir and oseltamivir groups in each age cohort had approximately equal percentages of male and female subjects. The Safety population from the 2 to <7 year-old cohort included 8 subjects between the age of 2 to <4 years (75% peramivir group; 25% oseltamivir group) and 26 subjects between the age of 4 to <7 years (85% peramivir group; 15% oseltamivir group).

Table 8.2.1-2: Demographics by Age & Treatment Group - Safety Population (Data Cutoff of March 2017)

	2 -<7 year-old cohort		7 -<13 year-old cohort		13 -<18 year-old cohort	
Baseline Characteristics	**Peramivir N=28**	**Oseltamivir N=6**	**Peramivir N=39**	**Oseltamivir N=9**	**Peramivir N=21**	**Oseltamivir N=7**
Sex, n (%)						
Male	15 (54%)	2 (33%)	19 (49%)	3 (33%)	12 (57%)	4 (57%)
Female	13 (46%)	4 (67%)	20 (51%)	6 (67%)	9 (43%)	3 (43%)
Age (years)						
Median (Q1–Q3)	5.1 (4.4–6.2)	4.8 (3.0–6.1)	9.1 (8.0–11.5)	9.1 (8.9–10.4)	16.6 (14.8–17.0)	16.6 (14.5–16.9)
Min, Max	2.3, 6.7	2.9, 6.6	7.2, 12.2	7.4, 12.9	13.1, 17.5	14.0, 17.7
Race, n (%)						
White	27 (96%)	6 (100%)	34 (87%)	9 (100%)	20 (95%)	7 (100%)
Black or African American	1 (4%)	0	4 (10%)	0	1 (5%)	0
Other	0	0	1 (3%)	0	0	0
Ethnicity						
Hispanic or Latino	7 (25%)	2 (33%)	9 (23%)	3 (33%)	6 (29%)	0
Not Hispanic/Latino	21 (75%)	4 (67%)	30 (77%)	6 (67%)	15 (71%)	7 (100%)
Weight (kg)						
Median (Q1–Q3)	19.1 (18.1–22.1)	18.5 (14.1–19.5)	34.0 (27.0–44.9)	36.8 (29.2–44.9)	75.7 (56.3–90.2)	61.0 (59.3–61.7)
Min, Max	13.6, 39.5	13.4, 25.4	21.3, 79.3	25.4, 71.2	48.4, 111.9	40.5, 62.6
Confirmed Influenza by RT-PCR						
Positive	26 (93%)	3 (50%)	30 (77%)	7 (78%)	13 (62%)	5 (71%)
Negative	2 (7%)	3 (50%)	9 (23%)	2 (22%)	8 (38%)	2 (29%)
Influenza type, n (%)						
A/H1N1	7 (25%)	2 (33%)	10 (26%)	3 (33%)	4 (19%)	4 (57%)
A/H3N2	9 (32%)	1 (17%)	7 (18%)	1 (11%)	2 (10%)	1 (14%)
A/Indeterminate	0	0	1 (3%)	0	0	0
B	6 (21%)	0	12 (31%)	3 (33%)	7 (33%)	0
A + B co-infection[a]	4 (14%)	0	0	0	0	0
Viral titer, n (%)						
Positive	22 (79%)	2 (33%)	27 (69%)	6 (67%)	12 (57%)	5 (71%)
Negative	6 (21%)	4 (67%)	12 (31%)	3 (33%)	9 (43%)	2 (29%)

[a] Influenza A + B co-infection included those with influenza A/H1N1 + B (n=1), influenza A/H3N2 + B (n=2), and influenza A/Indeterminate + B (n=1).

Source: Adapted from interim clinical study report and 90-day safety update report for Study BCX1812-305, Tables 14.1.4.3.3-90d , 14.1.4.3.4, and 14.1.4.3.5; Clinical reviewer's calculations.

8.2.2 Routine Clinical Testing

The safety assessments were considered sufficient. Routine clinical testing consisted of both clinical and laboratory evaluations. Clinical evaluations occurred at screening on Day 1, Day 3, Day 7, and Day 14. Laboratory evaluations occurred on Day 1 and Day 7.

8.2.3 Evaluation of Potential Adverse Events for Similar Drugs in Drug Class

The known safety profile of peramivir and other neuraminidase inhibitors (i.e., oseltamivir and zanamivir) were taken into consideration for this review. Please see Section 8.3.5 for Submission Specific Primary Safety Concerns.

8.3 Major Safety Results

8.3.1 Deaths

No deaths have occurred during Study BCX1812-305.

8.3.2 Nonfatal Serious Adverse Events

There have been no serious adverse events (SAEs) reported during Study BCX1812-305.

8.3.3 Dropouts and Discontinuations

Please see Section 7.3 for information related to subject disposition during Study BCX1812-305.

8.3.4 Significant Adverse Events

Please see Section 8.3.5 for Submission Specific Primary Safety Concerns and Section 8.4.1 for Common Adverse Events. No other significant adverse events were identified.

8.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest included neuropsychiatric events, rash, hypersensitivity reactions, infusion site reactions, hepatotoxicity, renal toxicity, hematological abnormalities, muscle injury, orthostatic hypotension/shock, and hemorrhagic colitis. These events were selected based on observations from the peramivir development program, the postmarketing experience with peramivir, and the safety labeling for other drugs in the neuraminidase inhibitor drug class (oseltamivir and zanamivir).

Neuropsychiatric events

Neuropsychiatric events were of special interest because events have been reported in the postmarketing setting with neuraminidase inhibitors, including peramivir. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. Events appear to be uncommon, but estimates of frequency cannot be made because events were reported voluntarily during clinical practice. Influenza itself can be associated with a variety of neurologic and behavioral events (i.e., hallucinations, delirium, and abnormal behavior) and definitive relationship between neuraminidase inhibitors and neuropsychiatric events has not been established. Regardless, the package inserts of peramivir, oseltamivir, and zanamivir contain precautionary language regarding abnormal behavior because there have been reports (mainly from Japan) of injury and death during the events.

Neuropsychiatric events in Study BCX1812-305 were reported in one (1%) peramivir-treated subject and two (9%) oseltamivir-treated subjects who had TEAEs in either the Nervous System Disorders System Organ Class (SOC) or Psychiatric Disorders SOC. The narratives for these subjects are summarized below:

- Subject 008.016 was an 11.0-year-old female without confirmed influenza infection who experienced moderate (Grade 2) psychomotor hyperactivity after peramivir treatment. Increased energy-hyperactivity was reported on Day 1, and the event resolved later that day. The event was considered probably not related to study drug by the investigator.

- Subject 020.014 was a 6.1-year-old female with confirmed influenza A/H1N1 infection who experienced moderate (Grade 2) hallucinations after oseltamivir treatment. Hallucination was reported after the first dose of oseltamivir on Day 1. Study drug was discontinued and the event resolved on Day 2. The subject discontinued the study on Day 5 because of the adverse event, which was considered probably related to study drug by the investigator.

- Subject 005.033 was a 17.7-year-old male with confirmed influenza A/H1N1 infection who experienced moderated (Grade 2) dizziness after oseltamivir treatment. Dizziness was reported on Day 6 and the event resolved on Day 13. The event was considered unlikely related to study drug by the investigator.

Rash

Rash was of special interest because severe rashes such as erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported during postmarketing experience for neuraminidase inhibitors, including peramivir.

No cases of severe cutaneous adverse reactions (i.e., erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis) were reported during Study BCX1812-305. Two (2%) subjects who received peramivir treatment had TEAEs in the Skin and Subcutaneous Tissue Disorders SOC; their narratives are summarized below:

- Subject 009.007 was a 17.3-year-old male without confirmed influenza infection who experienced severe (Grade 3) pyrexia, mild (Grade 1) pruritus, and mild (Grade 1) rash after peramivir treatment. On the morning of Day 3, the subject reported an isolated fever of 107°F that was treated with acetaminophen and ibuprofen. He presented to the clinic later that afternoon and had normal temperature. On examination, he had an itchy scalp and a rash on his neck and stomach. The events of pyrexia and pruritus resolved that day and the event of rash resolved the next day. The investigator considered the events of pyrexia and pruritus to be possibly related to study drug, while rash was considered not related to study drug.

- Subject 005.012 was an 11.6-year-old male with confirmed influenza B infection who experienced moderate (Grade 2) erythema after peramivir treatment. The subject had

skin redness on bilateral arms on Day 1 and the event resolved later that day. The event was considered unlikely related to study drug by the investigator.

Hypersensitivity reactions

Hypersensitivity reactions were of special interest because there have been reports with neuraminidase inhibitors, including peramivir, in the postmarketing setting. The clinical reviewer did not identify any case of hypersensitivity reaction during Study BCX1812-305.

Infusion site reactions

Infusion site reactions were of special interest because events have been reported in previous clinical trials of peramivir in adults. Notably, most of the TEAEs consistent with injection site reactions occurred with the intramuscular (IM) peramivir formulation.

Infusion site reactions during Study BCX1812-305 were reported in two (2%) peramivir-treated subjects who had TEAEs in the General Disorders and Administration Site Conditions SOC. The narratives for these subjects are summarized below:

- Subject 020.003 was a 9.7-year-old female without confirmed influenza infection who experienced mild (Grade 1) injection site paresthesia after peramivir treatment. The subject reported tingling of her right hand on Day 1 and the event resolved later that day. The investigator considered the event to be unlikely related to study drug.

- Subject 020.004 was a 13.1-year-old female without confirmed influenza infection who experienced mild (Grade 1) injection site coldness and mild (Grade 1) injection site rash after peramivir treatment. The subject reported coldness of her arm on Day 1 and the event resolved later that day. On Day 6, rash was reported at the IV site and this event resolved on Day 14. The investigator considered the event of injection site coldness to be unlikely related to study drug, while the event of injection site rash was considered to be definitely related to study drug.

Hepatotoxicity

Hepatotoxicity was of interest because liver enzyme abnormalities were frequently reported during the clinical development of peramivir in adults. A causal relationship between liver enzyme abnormalities and influenza is difficult to assess because influenza itself has also been associated with abnormal liver enzymes.

There were no clinical adverse events in the Hepatobiliary SOC reported during Study BCX1812-305. Two (2%) peramivir-treated subjects had elevated liver enzymes reported as adverse events. The narratives for these subjects are summarized below:

- Subject 009.019 was a 14.6-year-old male with confirmed influenza A/H1N1 infection who experienced the TEAEs of moderate ALT increased, severe AST increased, severe CK increased, and severe LDH increased after peramivir treatment. On Day 7, the subject had Grade 1 high ALT (125 U/L), Grade 4 high AST (508 U/L), Grade 4 high CK (20220 U/L), and high LDH (657 U/L, no DAIDS grading). He was asymptomatic and was reported to be playing basketball vigorously. The only concomitant

medication he reported taking was acetaminophen on Day 1 (2 doses) and Day 2 (1 dose). All four laboratory abnormalities were considered by the investigator to be possibly related to study drug. On Day 14, the subject's AST improved to high (not graded; 51 U/L), CK improved to Grade 1 high (1989 U/L), LDH improved to high (not graded; 254 U/L), and ALT was normal (44 U/L).

- Subject 020.025 was a 3.4-year-old male with confirmed influenza A/Indeterminate + B co-infection who experienced TEAEs of mild ALT increased, mild LDH increased, and mild serum bicarbonate decreased after peramivir treatment. This subject did not have clinical chemistry labs collected at baseline; however, the laboratory abnormalities of high AST (not graded; 46 U/L), high LDH (not graded; 448 U/L), and Grade 1 low serum bicarbonate (18 mEq/L) were noted on Day 9. The investigator considered the laboratory abnormalities to be not related to study drug. On Day 14, AST and LDH levels were normal, and serum bicarbonate remained Grade 1 low (19 mEq/L).

The liver chemistry data collected during Study BCX1812-305 are discussed in Section 8.4.2.

Renal Toxicity
Renal toxicity was of interest because of nephrotoxicity observed in rabbits in preclinical studies; however, this has not been observed in humans. No cases of renal failure or renal-related TEAEs were reported during Study BCX1812-305. The renal laboratory data collected during Study BCX1812-305 are discussed in Section 8.4.2.

Hematological abnormalities
Hematological abnormalities were of interest because neutropenia and leukopenia were frequently reported adverse events during the clinical development of peramivir. No cases of hematology-related TEAEs were reported during Study BCX1812-305. The hematology laboratory data collected during Study BCX1812-305 are discussed in Section 8.4.2.

Muscle injury
Muscle effects were of interest because transient increases in serum creatine kinase (CK) and creatine phosphokinase (CPK) were frequently reported during the clinical development of peramivir in adults. In some cases, adults who received the IM peramivir formulation had severe pain at the injection site as well as increased CK or CPK. Influenza itself has also been associated with rhabdomyolysis/myopathy.

There were no clinical adverse events in the Musculoskeletal and Connective Tissue Disorders SOC reported during Study BCX1812-305. On one occasion, a severe TEAE of CK increased was reported in a peramivir-treated subject (Subject 009.019). This subject, mentioned under hepatotoxicity events of interest, was asymptomatic and also had the TEAEs of AST, ALT, and LDH increased on the same day. The CK laboratory data collected during Study BCX1812-305 are discussed in Section 8.4.2.

Orthostatic hypotension or shock

Events of orthostatic hypotension and shock were of special interest because of reports from Japan during postmarketing experience with peramivir. Notably, an analysis of orthostatic hypotension in adults suggested that these events were probably vasovagal reactions related to dehydration, IV needle placement, and infusion rather than adverse reactions to peramivir. None of the prespecified orthostatic hypotension or shock preferred terms (i.e., blood pressure orthostatic decreased, procedural hypotension, orthostatic hypotension, syncope, presyncope, and loss of consciousness) was reported during Study BCX1812-305.

Hemorrhagic colitis

Hemorrhagic colitis was of special interest because it is listed in oseltamivir labeling as an event in the postmarketing setting. None of the prespecified hemorrhagic colitis preferred terms (i.e., diarrhea hemorrhagic, enterocolitis hemorrhagic, hematochezia, large intestinal hemorrhage, lower gastrointestinal hemorrhage, proctitis hemorrhagic, and rectal hemorrhage) were reported during Study BCX1812-305.

8.4 Supportive Safety Results

8.4.1 Common Adverse Events

Seventeen (19%) subjects in the peramivir group and 5 (23%) subjects in the oseltamivir group reported one or more TEAEs during Study BCX1812-305. Table 8.4.1-1 summarizes the common clinical adverse events reported as of the March 2017 data cutoff. Vomiting was the most common clinical adverse event reported in both the peramivir (3%) and oseltamivir (9%) groups. Three subjects, all in the 2 to <7 year-old cohort, had vomiting after peramivir treatment; these events were considered possibly related to study drug and resolved with no treatment. Among peramivir-treated subjects, no more than 1 subject in the same age cohort reported any of the other common clinical adverse events. Besides one subject who had severe (Grade 3) pyrexia, all clinical events in Study BCX1812-305 were reported as mild or moderate (Grade 1 or Grade 2). Given the low numbers of any one clinical event, labeling for Rapivab® will include all TEAEs occurring in ≥2% of pediatric subjects in the peramivir group.

Table 8.4.1-1: Summary of Treatment-Emergent Adverse Events Experienced by At Least 2 Subjects in Any Treatment Group – Safety Population (Data cutoff of March 2017)

Preferred Term	Peramivir N=88	Oseltamivir N=22	Total N=110
Vomiting	3 (3%)	2 (9%)	5 (5%)
Pyrexia	2 (2%)	0	2 (2%)
Tympanic membrane hyperemia	2 (2%)	0	2 (2%)
Nausea	0	2 (9%)	2 (2%)

Source: Adapted from Summary of Clinical Safety - 90-Day safety update report, Table 9.

8.4.2 Laboratory Findings

Twenty-nine subjects (33%) and 6 subjects (27%) in the peramivir and oseltamivir treatment groups, respectively, experienced one or more treatment-emergent laboratory abnormalities after receiving study drug. The most common laboratory abnormalities in the peramivir group were serum bicarbonate decreased (13%), proteinuria by dipstick analysis (8%), AST increased (5%), and decreased absolute neutrophil count (5%). The most common laboratory abnormality in the oseltamivir group was proteinuria by dipstick analysis (9%). The majority of abnormalities in the peramivir group were categorized as Grade 1 or Grade 2, and all of the abnormalities in the oseltamivir group were categorized as Grade 1.

Two (2%) peramivir-treated subjects experienced Grade 3 or Grade 4 laboratory abnormalities during Study BCX1812-305. Subject 009.019 experienced Grade 4 high AST, Grade 4 high CK, Grade 1 high ALT, and high LDH, all on the same day. The narrative for Subject 009.019 is summarized in Section 8.3.5. Subject 020.018 had Grade 3 low glucose, and the narrative for this subject is summarized below:

- Subject 020.018 was an 11.9-year-old female without confirmed influenza infection who received peramivir treatment and experienced Grade 3 low random glucose (34 mg/dL) on Day 9. The subject had no accompanying signs or symptoms of hypoglycemia and no urine ketones detected. The abnormality was not considered clinically significant and was thought to be a laboratory error by the Applicant.

Notable laboratory abnormalities, including hepatic-related, renal-related, hematology-related, and CK-related abnormalities, are discussed below. No new safety signals for peramivir were observed in this pediatric population.

Hepatic

Graded hepatic-related laboratory abnormalities during Study BCX1812-305 are summarized in Table 8.4.2-1. Five subjects (6%) in the peramivir group and 1 subject (5%) in the oseltamivir group had Grade 1 or higher hepatic-related abnormalities. The subjects with Grade 1 laboratory abnormalities did not have repeat LFTs after the Day 7 visit. On one occasion, a severe TEAE of AST increased and a moderate ALT increased were reported in Subject 009.019. This subject was asymptomatic and also had the TEAEs of increased CK and LDH on the same day. Subject 009.019 no longer had graded elevations in AST or ALT when levels were checked again at the Day 14 visit. Concomitant elevations in AST and ALT were noted in another peramivir-treated subject (Subject 006.004) who had Grade 1 AST and ALT elevations. No subjects, including subject 009.019, had elevations > 3 x ULN in AST or ALT in addition to >2 x ULN in total bilirubin and <2 x ULN in alkaline phosphatase. Therefore, no cases fulfilled criteria for Hy's law of drug-induced liver injury.

Table 8.4.2-1: Treatment-emergent Hepatobiliary Laboratory Abnormalities by Worst Grade Toxicity – Safety Population (Data cutoff of March 2017)

Laboratory Abnormality	Treatment	Maximum Toxicity Grade			
		1 n (%)	2 n (%)	3 n (%)	4 n (%)
AST increased	Peramivir	3 (3%)	0	0	1 (1%)
	Oseltamivir	1 (5%)	0	0	0
ALT increased	Peramivir	3 (3%)	0	0	0
Alkaline Phosphatase increased	Peramivir	1 (1%)	0	0	0
	Oseltamivir	1 (5%)	0	0	0

Source: Adapted from interim clinical study report and 90-day safety update report for Study BCX1812-305; Clinical reviewer's calculations.

Renal

Table 8.4.2-2 summarizes renal-related laboratory abnormalities reported in Study BCX1812-305. A total of 7 subjects (8%) in the peramivir group and 2 subjects (10%) in the oseltamivir group had Grade 1 or Grade 2 proteinuria. None of these subjects had urinalysis assessments repeated after the Day 7 visit. Rapivab® labeling will reflect that 3% of pediatric subjects treated with peramivir had Grade 2 proteinuria by dipstick analysis compared with zero in the oseltamivir group. No other renal-related laboratory abnormalities (i.e., hematuria assessed by quantitative RBCs and serum creatinine increased) were reported during the trial.

Table 8.4.2-2: Treatment-emergent Renal Laboratory Abnormalities by Worst Grade Toxicity – Safety Population (Data cutoff of March 2017)

Laboratory Abnormality	Treatment	Maximum Toxicity Grade			
		1 n (%)	2 n (%)	3 n (%)	4 n (%)
Urine Protein	Peramivir	4 (5%)	3 (3%)	0	0
	Oseltamivir	2 (9%)	0	0	0

Source: Adapted from interim clinical study report and 90-day safety update report for Study BCX1812-305; Clinical reviewer's calculations.

The clinical reviewer did not observe any clinically relevant changes in median serum creatinine values over time. No meaningful differences between treatment-groups or age-cohorts were observed with respect to changes in serum creatinine. As mentioned in Section 8.3.5, there were no cases of renal failure reported in either treatment group.

Hematology

No meaningful shifts in toxicity grade from baseline to Day 7 were observed in the majority of hematology parameters during Study BCX1812-305. The only exception was Grade 1 or Grade 2 neutropenia reported in 4 subjects (5%) in the peramivir group. Of these, only 1 subject (1%) had Grade 2 neutropenia. Leukopenia was not reported in either treatment group. As mentioned in Section 8.3.5, there were no cases of hematology-related TEAEs.

CK elevations

Graded treatment-emergent elevations in CK were noted in two (2%) peramivir-treated subjects during Study BCX1812-305. On one occasion, a severe TEAE of CK increased was reported in Subject 009.019. This subject was asymptomatic and also had the TEAEs of

increased AST, ALT, and LDH on the same day. The CK level improved to Grade 1 high when checked again at the Day 14 visit. Another subject had Grade 1 high CK, but this was an isolated laboratory abnormality and was not reported as an adverse event. As mentioned in Section 8.3.5, there were no cases of muscle-related clinical adverse events during Study BCX1812-305.

8.4.3 Pediatrics and Assessment of Effects on Growth

The Applicant did not conduct a formal assessment on the effects of peramivir on growth and development. No specific adverse event profile has been identified which would have major impact on growth of pediatric subjects. Further, as a single-dose drug, the potential of peramivir to significantly impact growth or development is considered low.

9. Postmarket Experience

The Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE) was consulted to search the FDA Adverse Event Reporting System (FAERS) database for pediatric cases of Rapivab® (peramivir injection). DPV searched the FAERS database for all pediatric cases from initial U.S. approval (December 19, 2014) through June 30, 2017. There were 10 pediatric adverse event cases identified and no deaths reported. The pediatric FAERS cases consisted of either labeled events or highly confounded events. In sum, DPV found no new pediatric safety signals for peramivir. Please refer to DPV/OSE review by Timothy Jancel, PharmD for complete details.

The Applicant also reviewed data from three open-labeled, non-controlled postmarketing surveillance studies performed in Japan (Shionogi postmarketing surveillance Study 1303-H148-04). The designs for these studies are summarized in Table 9-1.One postmarketing study was exclusive to pediatric patients <15 years old and included 1,199 patients in the safety analysis. The other two postmarketing studies were in the routine clinical setting or high-risk patients. The postmarketing study in the routine clinical setting included 69 pediatric patients <15 years old, and the postmarketing study in high-risk patients included 45 pediatric patients <15 years old. Adverse events reported in all three postmarketing studies were similar to events observed during development and no new pediatric safety signals were found. The postmarketing pediatric surveillance study had 5 SAEs of abnormal behavior, 5 SAEs of neutropenia, and 1 SAE each of loss of consciousness, rash, peripheral edema, and erythema multiforme. No SAEs were reported for the pediatric patients in the postmarketing routine clinical use surveillance study. In the postmarketing high-risk surveillance study, three pediatric patients experienced SAEs of neutropenia and 1 pediatric patient experienced an SAE of leukopenia. No deaths were reported for pediatric patients in any of these postmarketing surveillance studies.

Table 9-1: Japanese Postmarketing Surveillance Studies

Study Identifier	Study Design	Dosage Regimen; Route of Administration; Duration	Age Range; Number of Subjects (N)
Shionogi	Open-label, non-controlled	Daily dose of IV	Subjects <15 yrs

Study Identifier	Study Design	Dosage Regimen; Route of Administration; Duration	Age Range; Number of Subjects (N)
Postmarketing Study 1303-H148-04 in Pediatric Subjects	postmarketing surveillance study exclusively in pediatric subjects using consecutive case investigation method, from Oct 2010 to Feb 2012	peramivir: <100 mg: n=68 ≥100 - <200 mg: n=406 ≥200 - <300 mg: n=302 ≥300 mg: n=423 Duration of treatment: 1 day: n=1159 ≥2 days: n=40	old; Safety Population: N=1199
Shionogi Postmarketing Study 1303-H148-04 in Routine Clinical Use	Open-label, non-controlled postmarketing surveillance study exclusively in the routine clinical setting using consecutive case investigation method, from Oct 2010 to Feb 2012	Extent of exposure not specified	Subjects <15 yrs old; N=69
Shionogi Postmarketing Study 1303-H148-04 in High-Risk Subjects	Open-label, non-controlled postmarketing surveillance study in subjects with high risk factors using consecutive case investigation method, from Jan 2010 to Mar 2013	Extent of exposure not specified	Subjects <15 yrs old; N=181

Source: Adapted from Summary of Clinical Safety, Table 1.

10. Advisory Committee Meeting

An advisory committee meeting will not be held for this efficacy supplement.

11. Pediatrics

This application partially fulfills PREA PMR 2831-1 to study peramivir in pediatric patients from birth to <18 years of age:

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.

Trial Completion: 04/30/2018
Final Report Submission12/31/2018

The status of Study BCX1812-305 is ongoing. (b) (4) (b) (4).

12. Other Relevant Regulatory Issues

12.1 Inspections

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of three of the domestic clinical sites (sites No. 005, No. 020, and No.009). These sites were selected based on high patient accrual and the number of site specific protocol violations. Based on the inspections of the three clinical sites, the OSIS findings support the validity of the data reported in this supplemental NDA. The central bioanalytical laboratory where all pharmacokinetic samples were processed ((b) (4)) was not inspected during this review as the facility was inspected (b) (4) and classified NAI (No Action Indicated).

12.2 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206426/S-4

Submission Date(s): March 24, 2017

Applicant: BioCryst Pharmaceuticals, Inc.

Product: Rapivab (peramivir injection)

Reviewer: Mark Needles, M.D.

Date of Review: 08/24/2017

Covered Clinical Study (Name and/or Number): BCX1812-305

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 10		
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 ☐ N/A	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from applicant)

The applicant adequately disclosed information related to financial interest/arrangements for all the investigators who enrolled subjects into Study BCX1812-305 up to the March 2017 data cutoff. Clinical investigators were certified regarding the absence of financial interests and arrangements following requirements in 21 CFR 54.4(a)(1).

13. Labeling

Labeling negotiations were ongoing at the time this review was finalized. Below are some of the preliminary proposed modifications to the clinically-relevant sections of draft labeling.

1 INDICATIONS AND USAGE

RAPIVAB is indicated for the treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Acute Uncomplicated Influenza

Administer RAPIVAB within 2 days of onset of symptoms of influenza.

Adults and Adolescents (13 years of age and older)

The recommended dose of RAPIVAB in adult and adolescent patients 13 years of age or older with acute uncomplicated influenza is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes.

Pediatric Patients (2 to 12 years of age)

The recommended dose of RAPIVAB in pediatric patients 2 to 12 years of age with acute uncomplicated influenza is 12 mg/kg (up to a maximum dose of 600 mg), administered via intravenous infusion for 15 to 30 minutes.

2.2 Dosing in Patients with Renal Impairment

Table 1. Dosage Adjustment for Adults and Adolescents (13 years and older) with Altered Creatinine Clearance

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

*Calculated using Cockcroft and Gault equation.

Table 2. Dosage Adjustment for Pediatric Patients (2 to 12 years of age) with Altered Creatinine Clearance

	Creatinine Clearance*		
	≥50	**30-49**	**10-29**
Recommended Dose (mg)**	12 mg/kg	4 mg/kg	2 mg/kg

*Calculated using Cockcroft and Gault equation.
**Up to maximum dose of 600 mg

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Adverse Reactions in Adolescent and Pediatric Subjects (2 to 17 years of age)

Assessment of adverse reactions is based on a randomized, active-controlled study in which 110 adolescent and pediatric subjects ages 2 to 17 years of age with acute uncomplicated influenza received open-label treatment with a single dose of RAPIVAB (N=88), or 5 days of treatment with oseltamivir (N=22) *[See Use In Specific Populations (8.4) and Clinical Studies (14.2)]*.

The safety profile of RAPIVAB in subjects 2 to 17 years of age was generally similar to that observed in adults. Specific adverse reactions reported in pediatric subjects treated with RAPIVAB (occurring in ≥2% of subjects) and not reported in adults included vomiting (3% versus 9% for oseltamivir), fever and tympanic membrane erythema (2% versus 0%, respectively, for each of these events). The only clinically significant laboratory abnormality (DAIDS Grade 2) occurring in ≥2% of pediatric subjects treated with (b) (4) was proteinuria by dipstick analysis (3% versus 0% for oseltamivir).

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of RAPIVAB for the treatment of influenza has been established in pediatric patients 2 to 17 years of age. Use of RAPIVAB for this indication is supported by evidence from adequate and well-controlled trials of RAPIVAB in adults with additional data from Study 305, a randomized, active-controlled trial of 110 (b) (4) with acute uncomplicated influenza who received open-label treatment with a single dose of RAPIVAB or 5 days of treatment with oseltamivir administered within 48 hours of onset of symptoms of influenza *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*. Study 305 included:

- 13 to 17 years of age: 21 subjects treated with RAPIVAB 600 mg
- 2 to 12 years of age: 67 subjects treated with RAPIVAB 12 mg/kg (up to a maximum dose of 600 mg)

Safety and effectiveness of RAPIVAB in pediatric patients less than 2 years of age have not been established.

14 CLINICAL STUDIES

14.2 Acute Uncomplicated Influenza in Pediatric Subjects

Study 305 was a randomized, multicenter, open-label, active-controlled trial to evaluate the safety, pharmacokinetics and (b) (4) of a single intravenous dose of RAPIVAB administered for a minimum of 15 minutes in subjects 2 to 17 years of age with acute uncomplicated influenza who had fever greater than or equal to 37.8°C (oral) with at least one respiratory symptom (cough or rhinitis) or a positive influenza rapid antigen test.

Study treatment was started within 48 hours of onset of symptoms. Subjects were randomized to receive RAPIVAB 600 mg (13 to 17 years of age), RAPIVAB 12 mg/kg up to a maximum dose of 600 mg (2 to 12 years of age), or oral oseltamivir BID for 5 days. In addition, all enrolled subjects were allowed to take fever-reducing medications.

The overall efficacy population, consisting of subjects with confirmed influenza and administered study drug, totaled 84 subjects. Among the 69 subjects treated with RAPIVAB, the median age was 7.9 years; 55% were male; 58% were infected with influenza A virus, 36% were infected with influenza B virus, and 6% were co-infected with influenza A and B viruses.

The primary endpoint was the safety of peramivir compared to oseltamivir as measured by adverse events, laboratory analysis, vital signs and physical exams. Secondary endpoints included efficacy outcomes such as time to resolution of influenza symptoms and time to resolution of fever; however, the trial was not powered to detect statistically significant differences in these secondary endpoints. Subjects receiving RAPIVAB experienced a median time to alleviation of their combined influenza symptoms of 79 hours (interquartile range: 34-122 hours) compared to 107 hours (interquartile range: 57-145 hours) in subjects receiving oseltamivir. The median time to recovery to normal temperature (less than 37°C) was 40 hours (interquartile range: 19-68 hours) and 28 hours (interquartile range: 15-41 hours) in subjects receiving RAPIVAB and oseltamivir, respectively *[See Use In* Specific *Populations (8.4)]*.

14. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action***
  APPROVAL of the supplemental NDA is recommended.

- ***Risk Benefit Assessment***
  Although Study BCX1812-305 is not designed to formally test the efficacy of peramivir in pediatric subjects with acute uncomplicated influenza, the observed trends in clinical and antiviral outcomes (i.e., alleviation of influenza symptoms, resolution of fever, and reduction in viral shedding) are similar between peramivir and the comparator, oseltamivir. Further, the PK data collected in this trial demonstrate that the exposures achieved in pediatric subjects with the selected peramivir doses are within the range of exposures shown to be safe and effective in adults, thus permitting partial extrapolation of adult data to support the pediatric indication. Importantly, no new safety signals for peramivir were detected in pediatric subjects ages 2 to <18 years. In conclusion, the safety and efficacy results from Study BCX1812-305, in conjunction with adult data from adequate and placebo-controlled trials and the convenience of single-dose administration, support a favorable risk-benefit assessment of peramivir for the treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days.

- ***Recommendation for Postmarketing Risk Evaluation and Management Strategies***
  Postmarketing Risk Evaluation and Mitigation Strategy (REMS) will not be required. The applicant will continue to submit Periodic Adverse Drug Experience Reports (PAERs) and Development Safety Update Reports (DSURs) for review.

- ***Recommendation for other Postmarketing Requirements and Commitments***
  No additional PMRs or PMCs will be issued in response to this submission.

15. References

Blanton L, Alabi N, Mustaquim D, et al. Update: Influenza Activity in the United States During the 2016 – 17 Season and Composition of the 2017 – 18 Influenza Vaccine. MMWR Morb Mortal Wkly Rep 2017;66:668-676. DOI: http://dx.doi.org/10.15585/mmwr.mm6625a3.

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