CLINICAL PHARMACOLOGY REVIEW

NDA	206426 (S4)
Submission Type	Efficacy Supplement
Submission Date	03/24/2017
Generic Name	Peramivir
Brand Name	Rapivab™
Indication	Treatment of acute uncomplicated influenza
Dosage Form/ Strength	Solution for Intravenous infusion/10 mg/mL
Applicant	BioCryst Pharmaceuticals Inc.
Review Team	Simbarashe Zvada, Ph.D.; Jeffry Florian, Ph.D.; Islam R. Younis, Ph.D.

Background

This efficacy supplement contains safety, pharmacokinetics and effectiveness data to support expanding peramivir indication to include pediatric patients 2 to 17 years of age. The Applicant submitted this efficacy supplement in partial fulfillment of Post-Marketing Requirement (PMR) 283-1, which was issued at the time of peramivir initial approval on 12/19/2014.

The Applicant proposes a single infusion of peramivir at a dose of 12 mg/kg, up to a maximum dose of 600 mg, in pediatrics ≤ 12 years of age, and single infusion of peramivir at a dose of 600 mg in pediatrics 13 years of age and older. In support of the proposed dosing regimen, the Applicant submitted:

1. Interim results from an ongoing Phase 3 study (Study BCX1812-305) comparing safety, pharmacokinetics and effectiveness of peramivir IV to oral oseltamivir in pediatric subjects with acute uncomplicated influenza.
2. Results from a previously completed Phase 3 study (Study 0918T0633) of peramivir IV (10 mg/kg up to 600 mg once daily for 1-5 days) in Asian patients with type A or type B influenza who were between 28 days and 16 years of age.
3. A population PK analyses of the available pediatric peramivir concentration data.

Summary of Clinical Pharmacology Findings

Appropriateness of the proposed dosing regimen

The Applicant's proposed dosing of 600 mg in pediatrics 13 year of age and older and 12 mg/kg, up to a maximum of 600 mg, in pediatrics 2 to 12 years of age, administered as a single dose intravenously over 15 to 30 minutes is acceptable. Peramivir exposure following the administration of the proposed doses in pediatrics is comparable to peramivir exposure following the administration of 600 mg dose in adults (Figure 1, Table 3 in the appendix).

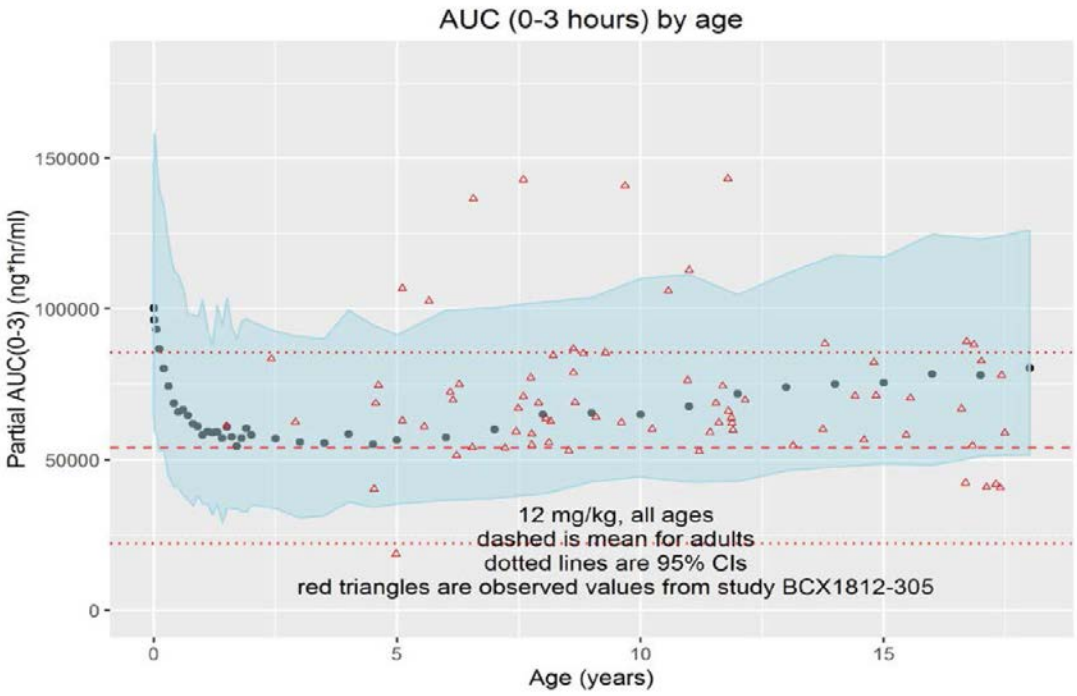

Figure 1. Simulated AUC(0-3 hours) after 12 mg/kg across all ages. (Source: Applicant's BCX1812-305 Population PKPD simulation report, Figure 29, page 42).

Dosing in Pediatric Subjects with Renal Impairment

No data in pediatrics subjects with renal impairment was provided in the submission. The applicant proposed dosing in pediatric subjects with renal impairment based on the dosing recommendation for adult subjects with renal impairment as follows:

1. Subjects with moderate renal impairment (Creatinine Clearance (CrCL) 30-49 mL/min): 200 mg in pediatrics 13 years of age and older and 4 mg/kg in pediatrics 2 to 12 years of age (one-third of the full dose)
2. Subjects with severe renal impairment (CrCL 10-29 mL/min): 100 mg in pediatrics 13 years of age and older and 2 mg/kg in pediatrics 2 to 12 years of age (one-sixth the full dose)

The proposal is acceptable because peramivir exposure in pediatric subjects is comparable to that observed in adults and renal maturation is attained by 2 years of age.

Labeling Recommendations

There are no clinical pharmacology related labeling changes.

Recommendations

The Office of Clinical Pharmacology recommends the approval of peramivir for the treatment of acute uncomplicated influenza in pediatric patients 2 to 17 years of age.

Appendix: Population Pharmacokinetic Review

The Applicant conducted a population PK analysis for peramivir following intravascular and intramuscular administration. The objective of this analysis was to develop a population PK model for peramivir and to use the developed model to simulate the exposures in pediatrics (area under the curve from 0 to 3 hours post dose [AUC 0-3]). The simulated exposures in pediatric subjects were compared with those observed in adults. The analysis utilized data from previous reports and new data from clinical trials conducted by the Applicant as described below under Materials and methods section.

Data Included in the POPPK Analysis

The previously reported clinical trials whose data was used in the population PK analysis are as follows:

1. **Study 0712T0611**: This was a Phase 1 study of single and repeated doses of peramivir IV in healthy adult Asian males. Doses were 100 mg QD, 200 mg QD, 400 mg QD and 400 mg BID. Subjects were dosed on Day 1, then Days 3 to 8. In each dose group six subjects received peramivir IV and 2 received placebo. Study 0712T0611 had predose samples on days 2-6.
2. **Study 0714T0612:** This was a Phase 1 clinical study of single and repeated dose peramivir IV in healthy adult Asian males. Six subjects received a single dose of peramivir IV 800 mg and 2 received placebo. Six other subjects subsequently received peramivir IV 800 mg once daily for 6 days and 2 received placebo. In study 0714T0612, subjects who received a single dose had rich PK sampling for 72 hours after a single dose. Subjects who received repeated doses had rich PK sampling for 24 hours after the first dose, followed by pre-dose samples on days 2-5. The final day of dosing was followed by 72 hours or rich sampling.
3. **Study 0722T0621:** This was a Phase 2 study of peramivir IV in adult Asian patients aged 20 to 64 years with symptoms of influenza and a positive Rapid Antigen Test (RAT) result. A single infusion of peramivir IV 300 mg, 600 mg, or placebo was administered. The study enrolled 300 patients (300 mg group, 99 patients; 600 mg group, 100 patients; and placebo group, 101 patients). Subjects in study 0722T0621 had sparse sampling (approximately 3 per subject) for 48 hours after the single dose.
4. **Study 0815T0631:** This was a Phase 3 study of peramivir IV in adult Asian patients aged 20 to 64 years with symptoms of influenza and a positive RAT. A single infusion of peramivir IV 300 mg, 600 mg, or oral oseltamivir (75 mg BID for 5 days) was administered. Seven hundred and twenty six subjects received peramivir. Study 0815T0631 included sparse sampling for 48 hours after the single dose.
5. **Study BCX1812-113:** This study compared the bioavailability of peramivir IV 600 mg to peramivir IM 600 mg. Twenty-four healthy subjects were enrolled in a two period crossover design study. Sampling for PK in study BCX1812-113 included rich sampling for 24 hours after both the IV and IM doses.
6. **Study BCX1812-212:** This study compared peramivir IM 600 mg as a single dose to placebo in patients with influenza. Four hundred two subjects were treated (202 received placebo, 200 received peramivir). Study BCX1812-212 included sparse sampling (approximately 2 samples per subject) for 48 hours after the single dose.
7. **Study BCX1812-311:** This study compared peramivir IM 300 mg as a single dose to placebo in patients with influenza. Fifty-seven patients received peramivir. Study BCX1812-311 included sparse sampling (approximately 2 samples per subject) for 48 hours after the single dose.

New clinical trials with data included in the population PK analyses are as follows:

1. **Study BCX1812-305:** This ongoing study compares peramivir IV to oral oseltamivir in pediatric subjects with acute uncomplicated influenza. Based on an interim analysis after the 2015/2016 influenza

season, seventy-eight patients received peramivir at a dose of 12 mg/kg (up to 600 mg). Up to 4 blood samples were collected from each patient with target sampling windows immediately following completion of infusion, 30 minutes to 1 hour post-infusion, 1 hour to 3 hours post-infusion, and 3 to 6 hours post-infusion.

2. **Study 0918T0633:** This was a Phase 3 study of peramivir IV (10 mg/kg up to 600 mg once daily for 1-5 days) in Asian patients with type A or type B influenza who were between 28 days and 16 years of age. One hundred seventeen patients received peramivir with 115 of those patients providing at least one PK sample. Of the 117 patients, 107 received a single dose of study drug and 10 patients received 2 days of study drug. Blood samples were collected just prior to the completion of the infusion, at least once between 30 minutes after the end of the infusion, prior to the start of the infusion on Day 2, and then once or twice more during the study.

The applicant performed the analysis using NONMEM 7.3 (ICON Development Solutions, Ellicott City, MD) using first-order conditional estimation with interaction (FOCE-I). Graphical analyses were performed using R, Version 3.3.1. Peramivir concentrations that were below the quantitation limit (BQL) were included according to the "M3" methodology in which BQL observations are treated as categorical data. The likelihood for BQL observations was maximized with respect to the model parameters, and the likelihood for an observation was taken to be the likelihood that it was indeed below the quantification limit. Subjects for whom all samples were BLQ were assumed to have received placebo, and were thus excluded from the analysis. The FOCE-I method, with LAPLACIAN and SLOW options were employed for all model runs. The clinical and demographic characteristics of pediatrics included in this analysis are summarized in Table 1.

Table 1. Subject Characteristics - Intent-to-Treat Population for Subjects with Samples for Inclusion in Pharmacokinetic Analysis

Age Cohort	Number of Subjects with PK Samples	Mean (SD) Age	Mean (SD) Dose (mg)
≥ 2 - < 7 years	28	5.0 (1.4)	246 (65)
≥ 7 - < 13 years	39	9.6 (1.7)	427 (120)
≥ 13 - < 18 years	20	15.9 (1.4)	600 (0)

Abbreviations: N/A = not applicable; PK = pharmacokinetic; SD = standard deviation
Source: Report BCX1812-305-PK

Bioanalytical Method

Quantitative determination of peramivir (BCX1812-305) in human plasma was accomplished by the use of solid-phase extraction (SPE) and high-performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) (Table 2). The linear range is 2.5 to 5000 ng/mL. The performance of the bioanalytical method is acceptable. Note that the Office of Study Integrity and Surveillance (OSIS) declined to inspect the bioanalytical facility because the facility was inspected in in [redacted] (b) (4) without identifying any significant observations (please refer to OSIS memo dated 08/24/2017.

Results

The final parameter estimates are shown Table 2 while the diagnostic plots are shown in Figure 1.

Table 2. Parameter estimates of final peramivir population PK model. (Source: Applicant's BCX1812-305 Population PKPD simulation report, Table1, page 11)

Parameter	Estimate	Bootstrap 95% CI
THETA[a](1) Central Volume of Distribution (liters/kg)	0.162	0.156, 0.170
THETA(2) Clearance (L/hr)	0.200	0.137, 0.287
THETA(3) Additive residual error term (ng/mL)	2.25	1.23, 272
THETA(4) Proportional residual error term	0.167	0.167, 16.7
THETA(5) Absorption rate constant (/hr) for IM dose	9.60	5.59, 16.8
THETA(6) K23 (/hr)	0.0295	0.0206, 0.0404
THETA(7) K32 (/hr)	0.0978	0.0690, 0.137
THETA(8) Effect of weight on Volume (power model)	1 FIXED	NA
THETA(9) Effect of CRCL on Clearance (linear additive)	1.29E-05	9.50E-06, 1.88E-05
THETA(10) Effect of race on Volume (proportional)	-0.0908[b]	-0.125, 0.0480
THETA(11) Effect of gender on Volume (power model)	0.00350	-0.0185, 0.0291[c]
THETA(12) Power for allometric scaling on Clearance	0.808	0.728, 0.892
THETA(13) Effect of age on Clearance for <3 years old (power model)	-0.178	-0.306, 0.0786
THETA(14) Effect of age on Clearance for >60 years old (power model)	-0.124	-0.183, 0.0777
THETA(15) K24 (/hr)	0.548	0.466, 0.624
THETA(16) K42 (/hr)	0.984	0.881, 1.07

[a]THETAs are the fixed effect parameters, e.g., volume, Ke, Ka
[b]A negative value suggests that the volume is decreased, proportionally, by 8.0% (1-exp(-0.0908)
c Significant by Likelihood Ratio Test but not by bootstrap CI.

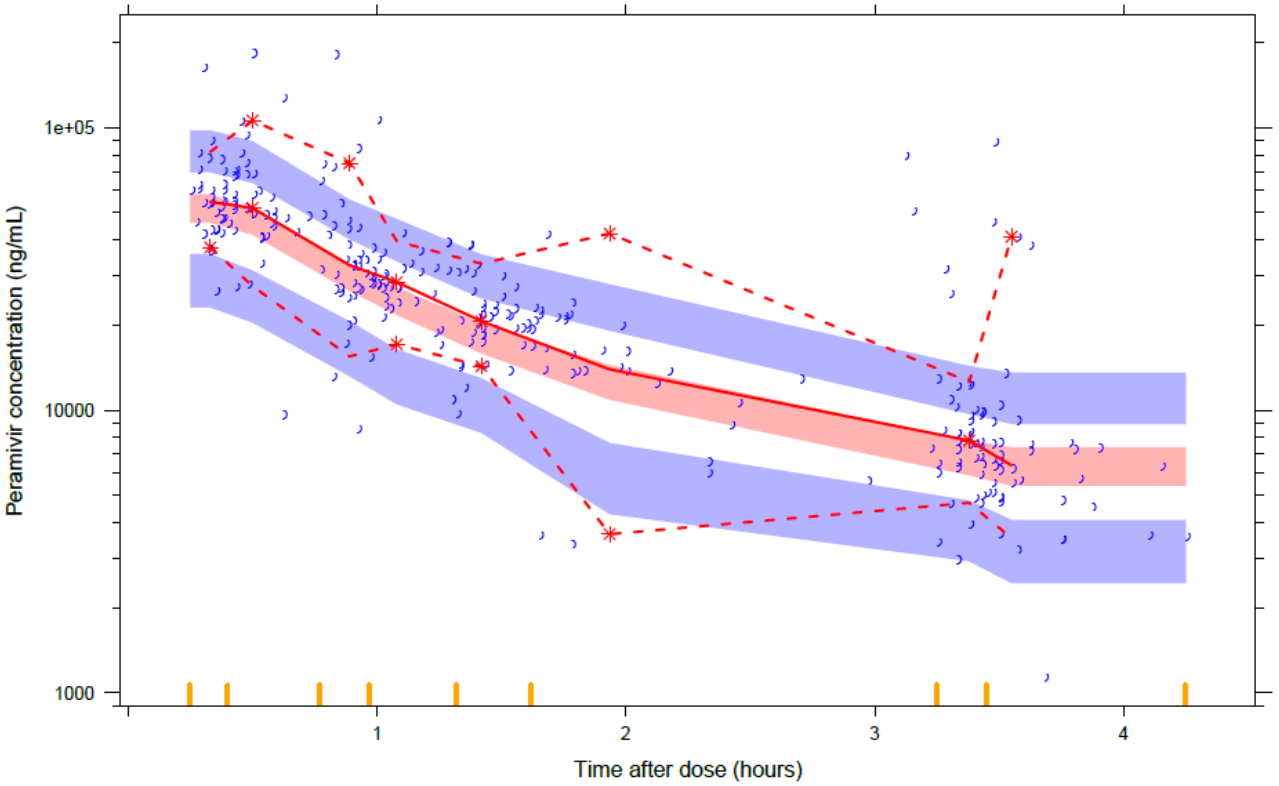

Figure 1. Visual predictive check for peramivir for Study BCX1812-305. Solid red line is the median of the observed data. Dashed red line is the upper and lower limits of the 95% range of the observed data. Red blocks are the 95% prediction interval for the simulated data. Blue blocks are the 95% prediction interval for the upper and lower limits of the 95% range.

Simulations for AUC comparisons

The applicant performed various simulations, to evaluate the different dosing regimens and used AUC (0-3 hours) for comparison of exposures between pediatrics and adults. The AUC (0-3 hours) was chosen since most the data used for PK analysis in Study BCX1812-305 was collected prior to this time point. This AUC chosen by the applicant is approximately 70% of AUC_{inf}. Figure 2 and Table 3 shows observed and simulated AUC (0-3 hours) comparisons and demonstrate substantial overlap across ages of 2 to 17 years of age.

In this final model, the applicant included data following intramuscular administration of peramivir for the population PK analysis, and the estimated parameter value for Ka of 9.6 per hour is strangely high. However, because we are using the model only for intravenous administration, this parameter value is of no consequence.

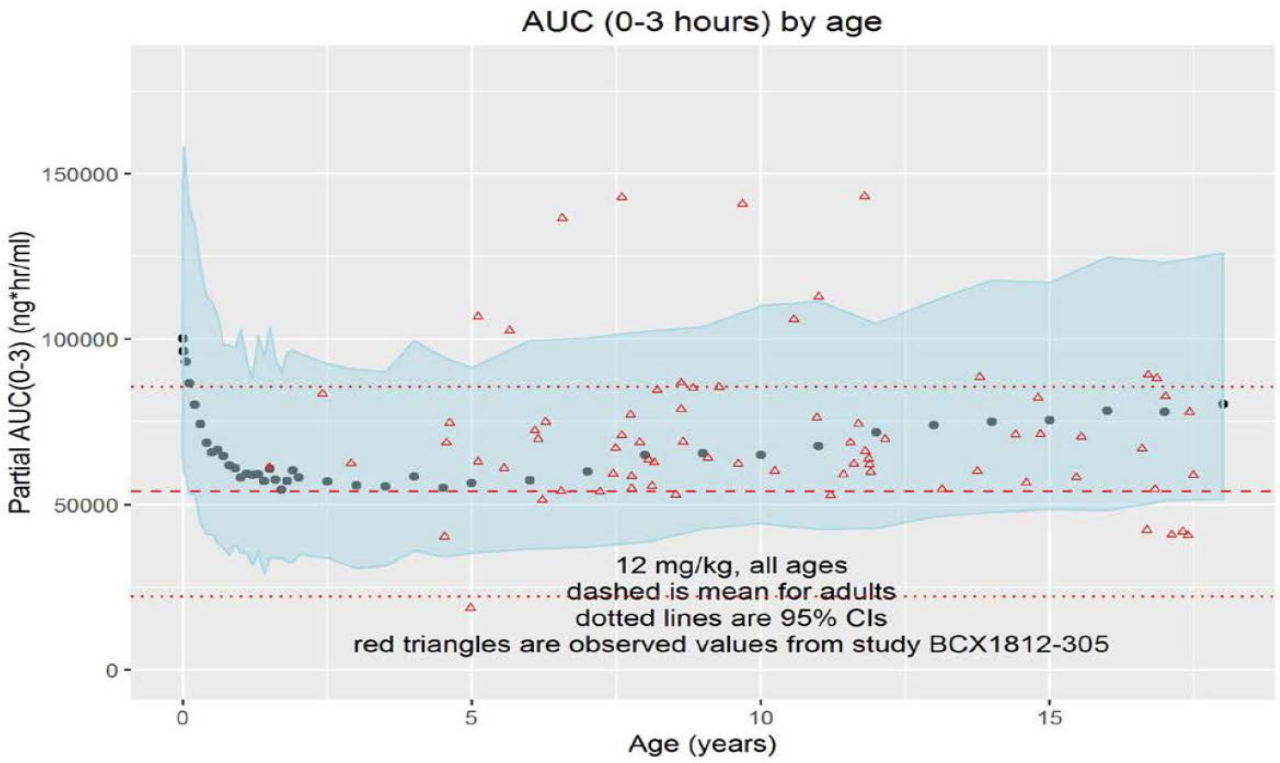

Figure 2. Simulated AUC(0-3 hours) after 12 mg/kg across all ages. (Source: Applicant's BCX1812-305 Population PKPD simulation report, Figure 29, page 42).

Table 3. Peramivir pharmacokinetic results - Intent-to-Treat population for subjects with samples for inclusion in pharmacokinetic analysis (2 to 17 year old population).

Age Cohort		**Cmax (ng/mL)**	**Tmax(h)[1]**	**Tlast (h)[1]**	**AUC_{0-3} (ng·h/mL)**
≥2 to < 7 years (n=28)	Mean (SD)	53600 (26200)	0.77 (0.32-3.5)	3.5 (0.48-4.4)	N/A
	Geometric Mean	47400	NA	NA	63100
	%CV	48.9	NA	NA	40.0
≥7 to <13 years (n=39)	Mean (SD)	66800 (35400)	0.47 (0.25-3.5)	3.5 (3.2-3.8)	N/A
	Geometric Mean	61200	NA	NA	76300
	%CV	53.0	NA	NA	43.1
≥13 to <18 years (n=20)	Mean (SD)	54300 (17900)	0.39 (0.28-0.63)	3.4 (3.3-4.2)	N/A
	Geometric Mean	51500	NA	NA	65500
	%CV	33.0	NA	NA	27.6
Adults study BCX1812-113	Mean (SD)	46800 (10100)	0.50 (0.50, 0.75)	NA	NA
	Geometric Mean	45700	NA	NA	68500
	%CV	21.5	NA	NA	19.1

Abbreviations: AUC_{last} = area under the plasma concentration versus time curve from time zero to the last measurable concentration; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; N/A = not applicable; T_{last} = time of last measurable plasma concentration; T_{max} = time to achieve C_{max}

[1] T_{max} and T_{last} were reported as median and [range]

Source: Report BCX1812-305-PK

Dose adjustments in pediatrics with renal impairment

No independent simulations for the impact of renal function in pediatrics were performed nor is there any data available in pediatric patients with renal impairment. Instead, the proposed dosing in children is a direct derivation of adult doses. The applicant claims that since the pharmacokinetics in pediatric subjects is comparable to that observed in adults, the same proportional dose reduction in pediatric patients is recommended. The reviewers agree with the applicant's approach and proposal.

Reviewer's Comments

Generally, the population pharmacokinetic model presented by the applicant is acceptable after evaluation of diagnostic plots. The pharmacokinetic model and simulations performed supports approval of peramivir use in pediatrics 2 to 17 years of age at the proposed doses. The argument by the applicant to use similar dose adjustments in pediatrics with renal impairment as in adults with renal impairment is acceptable given the similarity in exposures of peramivir in both adults and children. Also, even though no major differences are expected between the proposed dose adjustments in pediatrics 2 to 17 years old and adults, a more comprehensive approach is to simulate exposures for comparison of the full exposure profile (AUCinf).

Reviewer's Independent Assessment

Introduction

Population PK analysis for peramivir was included in this application to identify covariates which influence peramivir exposure. The primary objective was to evaluate whether the results from population PK analysis conducted by the applicant support the proposed pediatric dosing, which aims to achieve exposures in pediatrics similar to those in adults. The reviewer's analysis focuses on the comparison of AUC_{inf} between adults and children, and to evaluate the adequacy of proposed peramivir doses in pediatrics with impairment.

Methods

The datasets and characteristics of patients used in the analyses are summarized in the Table 4.

Table 4. Source for dataset and files used in the analysis

Description	File name	EDR Location
Final peramivir model Population PK datateset	peds-pk-20jul2017.txt finaldata-peds-20jul2017.xpt	\\CDSESUB1\evsprod\NDA206426\0074\m5\datasets\bcx1812-ppk-2\misc

The reviewer conducted the population PK analysis where estimation of typical population PK parameters, along with their random inter-individual variability (IIV) and inter-occasional variability (IOV), was performed in NONMEM 7.3 using a first-order conditional estimation method with ε–η interaction (FOCE INTER).

In order to compare the in order to compare the AUC_{inf} between adults and children, the final model from study BCX1812-305 was utilized. The datasets used for simulation were replicates of the original datasets used in population PK modeling in each study, to make a virtual population with at least a sample of 1000 individuals per age category. Only those subjects from studies with IV administration of peramivir were included in the analysis.

Results

The AUC_{inf} comparison across pediatric age categories and adults are summarized in the Table 5. The results are in agreement with what the applicant showed for AUC_{0-3}.

Table 5. Comparison of AUC_{inf} between pediatrics and adults

Age Cohort	Sample size	Geometric mean AUCinf, ng·h/mL (%CV)
2 to < 7 years	1008	86 977 (29.9)
7 to <13 years	1014	106 280 (27.8)
13 to <18 years	1000	92 280 (27.8)
Adults	1149	95 567 (46.4)

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/s/

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