CLINICAL PHARMACOLOGY REVIEW

NDA/SDN/Supplement	206426/178 (S-7)
Submission Type	Efficacy supplement
Applicant Name	BioCryst
Submission Date	7/29/2020
Generic Name	Peramivir
Brand Name	Rapivab
Dosage Form (Strength)	20 mg vial (10 mg/mL)
Indication	Treatment of acute complicated influenza
Review Team	Mario Sampson, PharmD, Vikram Arya, PhD, FCP

Prior to submission of this supplement, peramivir was approved for patients ≥2 years of age. This supplement contains results from trial BCX1812-305 (trial 305) in subjects six months - <2 years of age and revised labeling to extend approval to patients six months - <2 years of age.

Based on our review of trial 305 and the OSIS inspection of the analytical site which was favorable (NDA 206426, OSIS review dated 1/15/2021), we accept the trial 305 PK results for subjects six months - <2 years of age.

We identified no issues with the PK data in subjects six months - <2 years of age from trial 305. While mean AUC values were ~30% lower in subjects six months - <2 years of age vs adults (see section 2), based on exposure-response information we do not consider this exposure reduction to be clinically significant.

We agree with proposed 12 mg/kg dosing for subjects six months - <2 years of age and recommend approval of this supplement.

1 BCX1812-305

Objectives of trial 305 included safety, PK, effectiveness compared to oseltamivir, and incidence of influenza complications. Data from subjects aged 2 - <18 years of age from this trial were previously reviewed to support approval for ages 2 - <18 years. This review concerns data in subjects aged six months - <2 years.

Subjects six months - <2 years of age with eGFR ≥60 mL/min received a single 12 mg/kg dose of peramivir over a minimum of 15 minutes within 48 hours of onset of symptoms. Prohibited prior or concomitant medications were corticosteroids ≥10 mg/day. Planned PK sampling included four samples at the following timepoints: end of infusion; 30-60 minutes post-infusion; 1-3 hours post-infusion; 4-6 hours post-infusion. Concentrations of peramivir in plasma PK samples were measured using method BACG-3962.

Protocol deviations

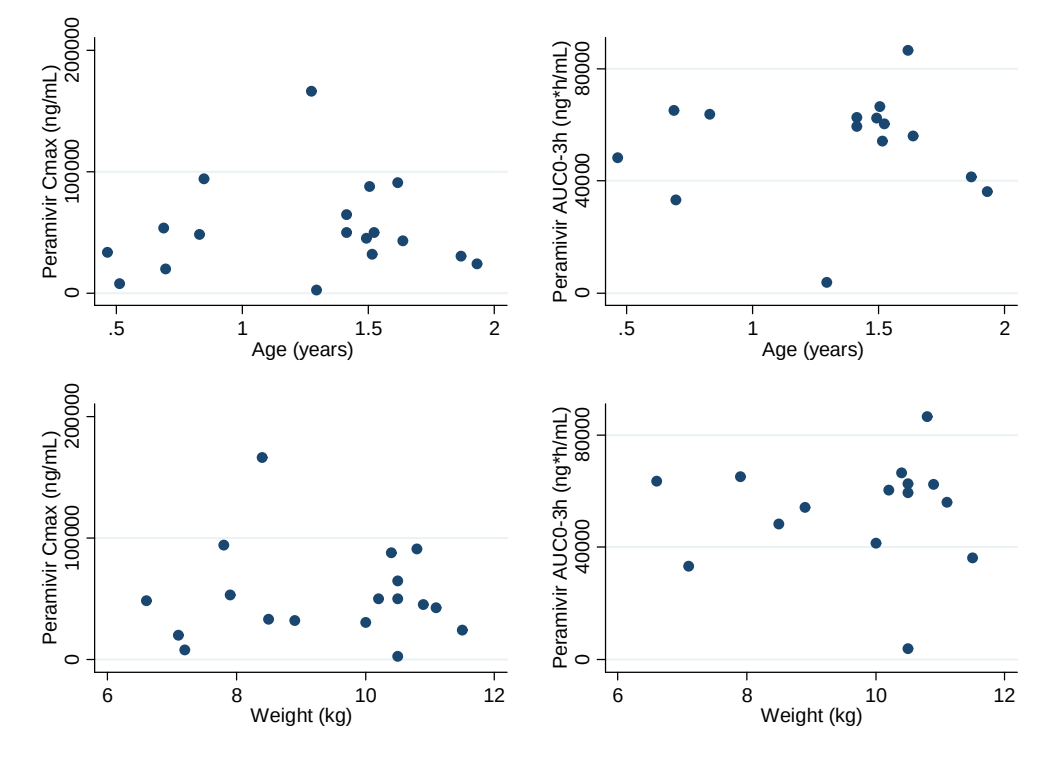
Twenty protocol deviations were reported. Most common were missed samples (n=6 for nasal swab, n=2 for urine) or paperwork issues (n=4). One deviation related directly to PK analysis

where an expired PK lab kit was used. Overall, in our assessment, protocol deviations are not expected to affect the PK results.

Pharmacokinetics

PK parameters were calculated using noncompartmental analysis. In the peramivir arm, C_{max} was reported for 18 subjects and AUC_{0-3h} for 15 subjects. There was no relationship between exposure and age or weight which supports the same mg/kg dose for the six months to < 2 years age group. (Figure 1).

Figure 1. Peramivir C_{max} and AUC_{0-3h} vs age or weight in subjects six months - <2 years of age in trial 305.

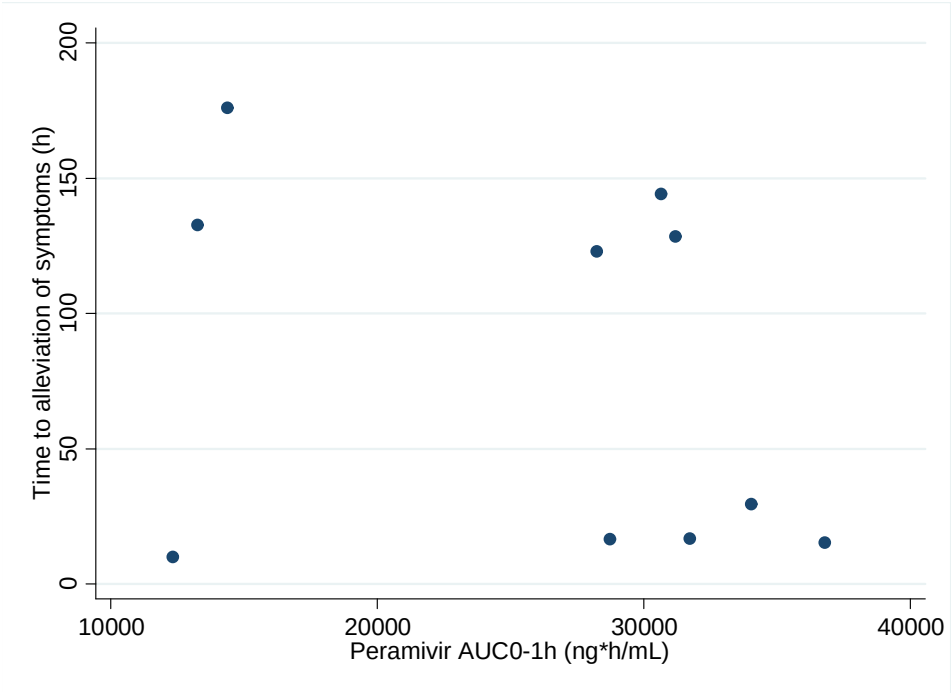


Source: Prepared by Reviewer.

Exposure-response assessment

Time to alleviation of symptoms (TTAS) was reported for 10 of 18 subjects six months - <2 years of age with peramivir PK data. TTAS was not reported for any of the six subjects six months - <2 years of age enrolled at site (b) (6) There was no association of TTAS with AUC_{0-1h} (Figure 2). Of note, AUC_{0-1h} (instead of AUC_{0-3hr}) from trial 305 was used for exposure-response assessment because only AUC_{0-1hr} was available from adult phase 3 trial BCX1812-306 (trial 306) to identify the range of exposures associated with efficacy (section 2). TTAS was not reported for the two subjects with lowest AUC_{0-1h}, which were the subjects with AUC_{0-1h} below the adult 5th percentile.

Figure 2. TTAS versus peramivir $AUC_{0\text{-}1h}$ in subjects six months-<2 years of age in trial 305.



Source: Prepared by Reviewer. Subject with TTAS = -0.4 not shown (also excluded in the Applicant's analysis).

Bioanalytical methods

Concentrations of peramivir in plasma PK samples were measured using method BACG-3962. The calibration range is 25-50000 ng/mL and duration of stability is three months at -80°C. Carryover was observed, with peramivir peak areas in blank samples equal to ~20% of the peak area at the LLOQ. However, no peramivir concentrations in subjects six months - <2 years of age were near the LLOQ of 25 ng/mL.

While the duration of stability is three months at -80°C, the maximum time between sample collection and analysis was 406 days (Table 1, Table 2). Using a different method with a calibration range of 2.5-5000 ng/mL, peramivir long-term stability was demonstrated at -80°C for 27 months (NDA 206426, response to IR submitted 1/19/2021). Most peramivir plasma concentrations in subjects six months - <2 years of age exceeded 5000 ng/mL (Table 1). However, the OSIS reviewer concluded that higher peramivir concentrations would be unlikely to affect duration of stability and recommended accepting the analytical results from the trial (see OSIS review dated 1/15/2021).

Table 1. Time between PK sample collection and analysis in subjects aged six months - <2 years in study BCX1812-305.

Subject ID	Timepoint (hours)	Collection date and time	Collection date	Analysis date	Peramivir concentration (ng/mL)	Time between collection and analysis (days)
BCX1812-305 (b) (6)	0	(b) (6) Γ13:50		(b) (6)	32100	51
BCX1812-305	0.5	Γ14:36			19900	51
BCX1812-305	1	Γ15:12			14400	51
BCX1812-305	3	Γ16:55			6060	51
BCX1812-305	0	Γ10:55			20000	357
BCX1812-305	0.5	Γ11:48			12100	357
BCX1812-305	1	Γ13:10			6610	357
BCX1812-305	3	Γ14:40			2660	357
BCX1812-305	0	Γ14:05			45100	
BCX1812-305	0.5	Γ14:31			30100	
BCX1812-305	1	Γ15:05			19700	
BCX1812-305	3	Γ17:00			6670	
BCX1812-305	0	Γ16:20			49900	80
BCX1812-305	0.5	Γ16:55			25800	80
BCX1812-305	1	Γ17:32			17800	80
BCX1812-305	3	Γ19:20			5450	80
BCX1812-305	0	Γ12:15			33300	68
BCX1812-305	0.5	Γ13:00			18400	68
BCX1812-305	1	Γ14:05			11500	68
BCX1812-305	3	Γ15:13			5960	68
BCX1812-305	0	Γ13:17			53300	131
BCX1812-305	0.5	Γ13:50			29000	131
BCX1812-305	1	Γ14:30			16700	131
BCX1812-305	3	Γ16:15			8180	131
BCX1812-305	0	Γ18:37			49700	97
BCX1812-305	0.5	Γ19:14			22200	97
BCX1812-305	1	Γ19:34			18300	97
BCX1812-305	3	Γ21:42			5570	97
BCX1812-305	0	Γ19:27			64700	406
BCX1812-305	0.5	Γ19:58			24600	406
BCX1812-305	1	Γ20:36			14900	406
BCX1812-305	3	Γ22:35			4860	406
BCX1812-305	0	Γ16:29			42800	385
BCX1812-305	0.5	Γ17:00			28400	385
BCX1812-305	1	Γ17:28			16800	385
BCX1812-305	3	Γ19:45			4240	385
BCX1812-305	0	Γ11:35			48400	111
BCX1812-305	0.5	Γ12:10			27200	111
BCX1812-305	1	Γ13:20			12800	111
BCX1812-305	3	Γ14:35			6270	111
BCX1812-305	0	Γ16:05			18300	368

	(b) (6)		(b) (6)		(b) (6)		
BCX1812-305		0.5		T16:35		24000	368
BCX1812-305		1		T17:08		11600	368
BCX1812-305		3		T19:02		4420	368
BCX1812-305		0		T12:53		1140	85
BCX1812-305		0.5		T13:30		30400	85
BCX1812-305		1		T14:40		10600	85
BCX1812-305		3		T15:53		10300	85
BCX1812-305		0		T13:51		7690	219
BCX1812-305		1		T15:20		7180	219
BCX1812-305		0		T12:40		2330	212
BCX1812-305		0.5		T13:10		1510	212
BCX1812-305		1		T13:45		1310	212
BCX1812-305		3		T15:48		583	212
BCX1812-305		0		T13:10		166000	211
BCX1812-305		0.5		T13:45		4860	211
BCX1812-305		0		T12:23		90700	206
BCX1812-305		0.5		T13:00		35100	206
BCX1812-305		1		T14:20		9290	206
BCX1812-305		3		T15:20		1770	206
BCX1812-305		0		T13:07		87600	206
BCX1812-305		0.5		T13:40		22200	206
BCX1812-305		1		T14:10		7650	206
BCX1812-305		3		T16:00		6360	206
BCX1812-305		0		T13:10		93900	154
BCX1812-305		0.5		T13:40		13700	154
BCX1812-305		1		T14:20		4040	154

Source: Prepared by reviewer from bioanalytical report.

Table 2. Assessment of method BACG-3962 performance in trial 305.

Method	Major deviations	Accuracy and precision values of calibration and QC samples within 15% (20% at LLOQ)	Max time between sample collection and analysis	Samples measured within the duration of stability	Incurred sample reanalysis pass rate (within 30% of original measurement)	Chromatograms
BACG3962	None	Yes	406 days	Yes	Yes	No anomalies observed

Source: Prepared by reviewer from bioanalytical report.

2 Comparison of exposures in subjects six months - <2 years of age versus adults

Similarity of exposures in ages six months -<2 years vs adults is the basis of approval.

PK data from healthy adults administered 600 mg IV in trial BCX1812-113 (trial 113) was used as the adult reference in the previous pediatric approval in ages two - <18 years and for this supplement for ages six months - <2 years. The geometric mean ratio (GMR) and 90% confidence intervals (CI) for age six months - <2 years vs adults (trial 113) for AUC_{0-3h} was 0.68 (0.52, 0.88) and for C_{max} was 0.83 (0.59, 1.18) (Data analyses submitted 11/16/2020).

To interpret the ~30% lower AUC values in age six months - <2 years vs adults, we evaluated the range of exposures associated with efficacy in Phase 3 trials. Trial 0722T0621 (trial 621) in adults with acute uncomplicated influenza was completed in 2008 and is described in labeling. While PK was assessed in this trial, PK parameters were not reported in the study report and plasma peramivir concentrations had to be adjusted by 11.5% to account for losses: "It has been reported that there will be losses of 11.5% of the total administered amount when using the intravenous infusion route for the preparations used in this study" (0722T0621 CSR). Also, the Clinical Pharmacology review of the original NDA does not report trial 621 PK parameters or an exposure-response analysis (NDA 206426 Clinical Pharmacology review dated 8/22/2014). The Applicant suggested use of single arm trial BCX1812-306 (trial 306) to evaluate exposure-response and the range of exposures associated with efficacy. In trial 306, elderly subjects with acute uncomplicated influenza received the approved 600 mg IV dose of peramivir. Up to three PK samples were collected with the last timepoint being 1-3h post-infusion. AUC_{0-3h} could not be calculated; AUC_{0-1h} was used instead. In this trial, peramivir AUC_{0-1h} was not associated with time to alleviation of symptoms (TTAS) (Table 3). Two subjects six months - <2 years of age in trial 305 had AUC_{0-1h} values below the 5th percentile of AUC_{0-1h} in adults in trial 306; no subjects six months - <2 years of age in trial 305 had AUC_{0-1h} below the adult (trial 306) minimum AUC_{0-1h} value (Figure 3, response to IR submitted 12/1/2020). Of note, there was no significant difference in exposures between healthy adults given peramivir 600 mg IV in trial 113 vs elderly adults with acute uncomplicated influenza given 600 mg IV in trial 306 (AUC_{0-1h} GMR [90%] CI: 0.94 [0.75, 1.18], response to IR submitted 12/1/2020).

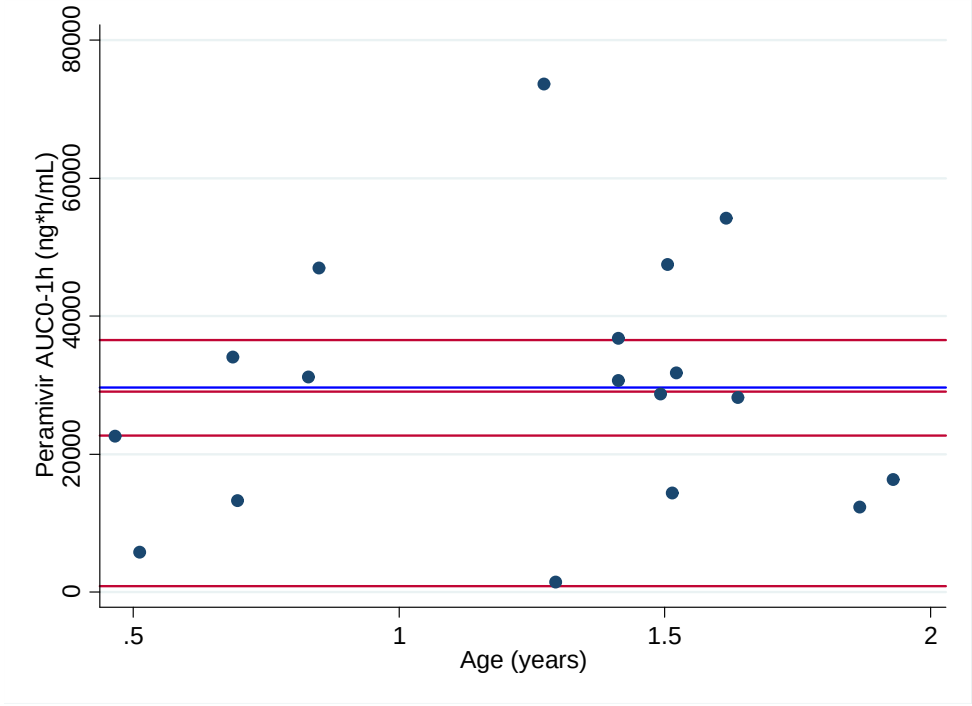
Based on exposures in subjects six months -<2 years of age being within the range of adult exposures in trial 306, no association of TTAS with AUC in trial 306, and similarity of exposures between healthy adults and adults with acute uncomplicated influenza, we do not consider the ~30% reduction in AUC values in subjects six months -<2 years of age vs healthy adults in trial 113 to be clinically significant.

Table 3. Trial 306 peramivir AUC_{0-1h} values in relation to TTAS.

	Minimum and maximum AUC_{0-1h} within quartile (Q)	Median TTAS (hours)
Q1 (n=12)	884.6, 22720	130.1
Q2 (n=12)	22720, 29030	111.6
Q3 (n=12)	29030, 36520	92.9
Q4 (n=15)	36520, 554800	114.2

Source: Data analyses submitted 11/16/2020, Response to IR submitted 11/16/2020.

Figure 3. $AUC_{0\text{-}1h}$ in subjects six months - <2 years of age in trial 305 vs adults in trial 306.



Source: Prepared by Reviewer. Red lines = adult min, Q1, median, and Q3. Adult max (554800 ng*h/mL) was an outlier and not plotted. Blue dots = individual subjects aged six months - <2 years; Blue line = median in ages 6 months-<2 years.

3 Labeling

Section 8 Renal impairment

Subjects with eGFR <60 mL/min were to be excluded from trial 305. Among subjects six months - <2 years of age, one subject had eGFR values <60 mL/min (NDA 206426, response to IR submitted 1/6/2021). Per labeling, peramivir requires dose adjustment for patients with eGFR <50 mL/min. We agree with the following statement added to section 8 of labeling: "No data are available for RAPIVAB use in pediatric patients six months to less than 2 years with creatinine clearance less than 50 mL/min to inform a recommendation for dosage adjustment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]."

Section 12.3 Pediatrics

Per our recommendation, labeling shows PK parameters by pediatric age group and geometric mean ratios for comparison of exposures in subjects <2 years of age vs adults.

Table 4. Peramivir PK parameters in subjects six months-<2 years of age vs adults from draft labeling.

Age Group	GM C_{max} (ng/mL) (%CV)	GM AUC_{0-3} (ng.h/mL) (%CV)
6 months to < 2 years	38000 (73.7)	46200 (35.8)
2 to < 7 years	47400 (48.4)	62700 (39.7)
7 to < 13 years	61200 (53)	76300 (43.1)
13 to < 18 years	51500 (33)	65500 (28.1)
Healthy Adults (Study 113)	45,700 (21.5)	68,500 (19.1)

In pediatric patients 6 months to less than 2 years of age, the GM C_{max} and AUC_{0-3} were lower than that of healthy adult subjects, with GM ratio (90% CI) (b) (4) (b) (4) respectively. The difference in exposure is not considered to be clinically significant.

Source: Draft labeling submitted 12/23/2020.

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/s/

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