Office of Clinical Pharmacology
Division of Pharmacometrics Review

NDA Number	021038 S-027 (PMR 1772-1)
Submission Date	6/17/2022
Submission Type	NDA Supplement
Drug Components	Dexmedetomidine HCl (DEX)
Proposed dosing	For Pediatric Procedural Sedation: • Patients 1 month to less than 2 years old initiate at 1.5 mcg/kg over 10 minutes followed by a maintenance infusion of 1.5 mcg/kg/hour and titrated to achieve desired clinical effect with dosage ranging from 0.5 to 1.5 mcg/kg/hour; • patients 2 to 16 years old initiate at 2.0 mcg/kg over 10 minutes followed by a maintenance infusion of 1.5 mcg/kg/hour and titrated to achieve desired clinical effect with dosage ranging from 0.5 to 1.5 mcg/kg/hour. A reduction in Precedex dosage should be considered if clinically indicated.
Proposed Indication	Sedation of non-intubated pediatric patients aged 1 month to 16 years prior to and during non-invasive procedures
Applicant	Pfizer/Hospira
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D., Yun Xu, Ph.D. (TL)
Pharmacometrics Reviewer	Jie Liu, Ph.D., Atul Bhattaram, Ph.D. (TL)

1 Summary of Findings

Clinical Pharmacology Recommendations: The submission is acceptable from a clinical pharmacology perspective. This review confirms the previous labeling recommendations in "Section 12.3 Pharmacokinetics – Pediatrics" as described below.

Regulatory Background: Dexmedetomidine HCl (Precedex™; hereafter referred to as DEX) was approved by FDA on 17 December 1999 (NDA 21038) for the sedation of initially intubated and mechanically ventilated adult patients during treatment in an intensive care setting for up to 24 hours. DEX was also approved by the FDA on 17 October 2008 for sedation of non-intubated adults prior to and/or during surgical and other procedures. In 2008 following FDA approval of DEX for procedural sedation in adults, Hospira received a PREA requirement to conduct a clinical study in pediatric participants. In response, Hospira conducted Study DEX-10-16. Additionally, DEX PK in pediatrics has been extensively evaluated through a pediatric written request (see clinical pharmacology review dated 5/23/2013 by Drs. Srikanth C. Nallani, Satjit Brar, Venkatesh A. Bhattaram and Yun Xu).

The applicant submitted the USPI reflecting the results of Study DEX-10-16 to the FDA in October 2015. However, the FDA concluded that the study had failed to fulfill the PREA requirement because the design of Study DEX-10-16 was inadequate for evaluating the efficacy and safety of DEX in pediatric patients undergoing treatment requiring sedation. Thus, a new pediatric study with demographically diverse patient population and an analysis for drug-demographic interactions were required by the FDA.

This application was submitted to fulfil PREA PMR 1772-1. The applicant conducted study C0801039 to investigate the safety and efficacy of DEX for sedation during treatment in pediatric participants undergoing MRI to address the FDA's comments. In this submission, a population PK evaluation of DEX infusion in Japanese pediatric participants in the ICU was conducted in Study C0801017 with a total of 308 DEX PK observations from 46 Japanese pediatric participants (from ≥45 weeks corrected gestational age to <17 years old).

Of note, the sponsor submitted a partial waiver request for birth to 1 month of pediatric patients; effectively, the indication sought is for the age of 1 month to <17-year pediatric patients.

The applicant's submitted population PK (popPK) results can be reproduced during the review. In summary, PopPK model from the global studies is appropriate to describe DEX PK in Japanese pediatric participants. Estimated individual PK parameters in Japanese pediatric patients using the final population PK model from the global studies were within the range of those in non-Japanese pediatric patients, suggesting the PK similarity between these populations.

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Have a demographically diverse patient population and an analysis for drug-demographic interactions been included as requested in the Agency's CRL (dated August 8, 2016) in the applicant's submission?

As stated above, DEX PK in pediatrics have been extensively evaluated and previously reviewed by clinical pharmacology team.

Study C0801039 was a Phase 3/4 randomized, double-blind, dose-ranging study of the safety and efficacy of DEX used with PRO as needed for procedural sedation of pediatric participants ≥1 month to <17 years of age undergoing MRI scans. PK samples were not collected in the study.

A total of 122 participants were included in the safety population analysis set, with 34 of the 122 (28%) being enrolled in Japan. Demographic analysis of the participants shows that the study

included a demographically diverse patient population (**Table 1**).

A population PK evaluation of DEX infusion data for mechanically ventilated pediatric participants was performed for 4 global PK studies (Study DEX-09-08, the CHOP study, Study DEX-08-01, and Study DEX-11-01) to evaluate the effect of intrinsic factors and it was previously reviewed by the FDA reviewer (Clin Pharm Review dated 5/23/2013). The effect of sex and ethnicity were not identified as statistically significant predictors of DEX PK variability (Figure 1).

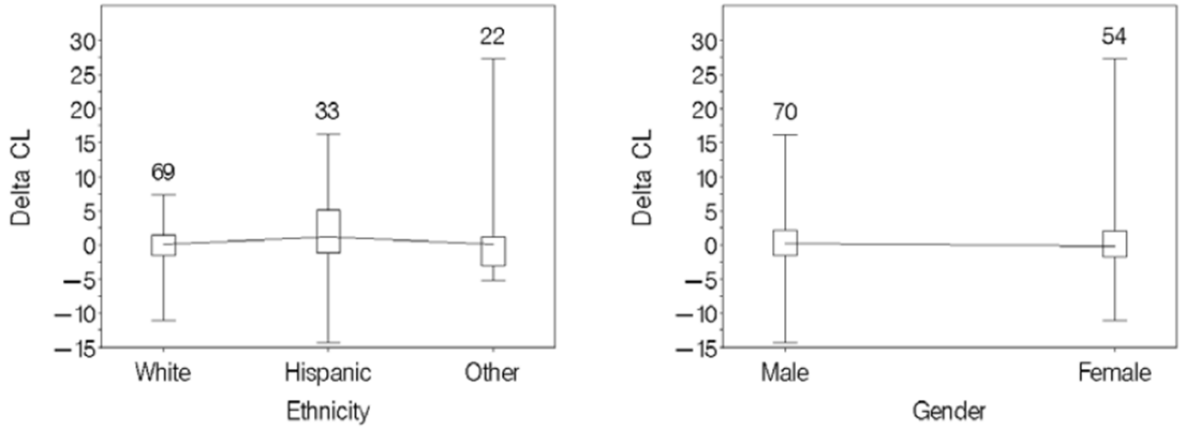
Table 1. C0801039 Study Level Diversity Data – Safety Population Set

Category	Diversity/ Demography	Count	Percent[a]	US Census[b]
Ethnicity	Hispanic or Latino	19	22.35%	18.50%
	Not Hispanic or Latino	66	77.65%	81.50%
	Not Reported	3		
Race	Asian	7	8.86%	5.90%
	Black or African American	8	10.13%	13.40%
	American Indian or Alaska Native	2	2.53%	1.30%
	Multiple	4	5.06%	2.80%
	White	57	72.15%	76.30%
	Native Hawaiian or Other Pacific islander	1	1.27%	0.20%
	Not Reported	9		
Sex	Female	43	48.86%	50.80%
	Male	45	51.14%	49.20%

a. Not reported subjects are excluded from percentage calculation.
b. US census outcome based on July 2021 data.

Source: The applicant's response to FDA CRL, NDA 021038/S-028 – Post Marketing Requirement (PMR) 1772-1, Page 6, Table 2

Figure 1. Delta-Parameter Versus Covariate Plots for Dexmedetomidine Clearance and Volume of the Central Compartment, Based on the Final Base Structural Model



Source: Dex-PK-Modeling Report, Page 242, Appendix.5

In addition, the estimated individual PK parameters in Japanese pediatric patients using Cognigen PopPK model were within the range of those in non-Japanese pediatric patients, suggesting the PK similarity between these populations (**Figure 2**).

2. APPLICANT'S ANALYSIS

2.1 OBJECTIVES

• To characterize the PK profile of dexmedetomidine in Japanese pediatric subjects in the intensive care unit (ICU).
• To compare the PopPK parameters in Japanese and non-Japanese.

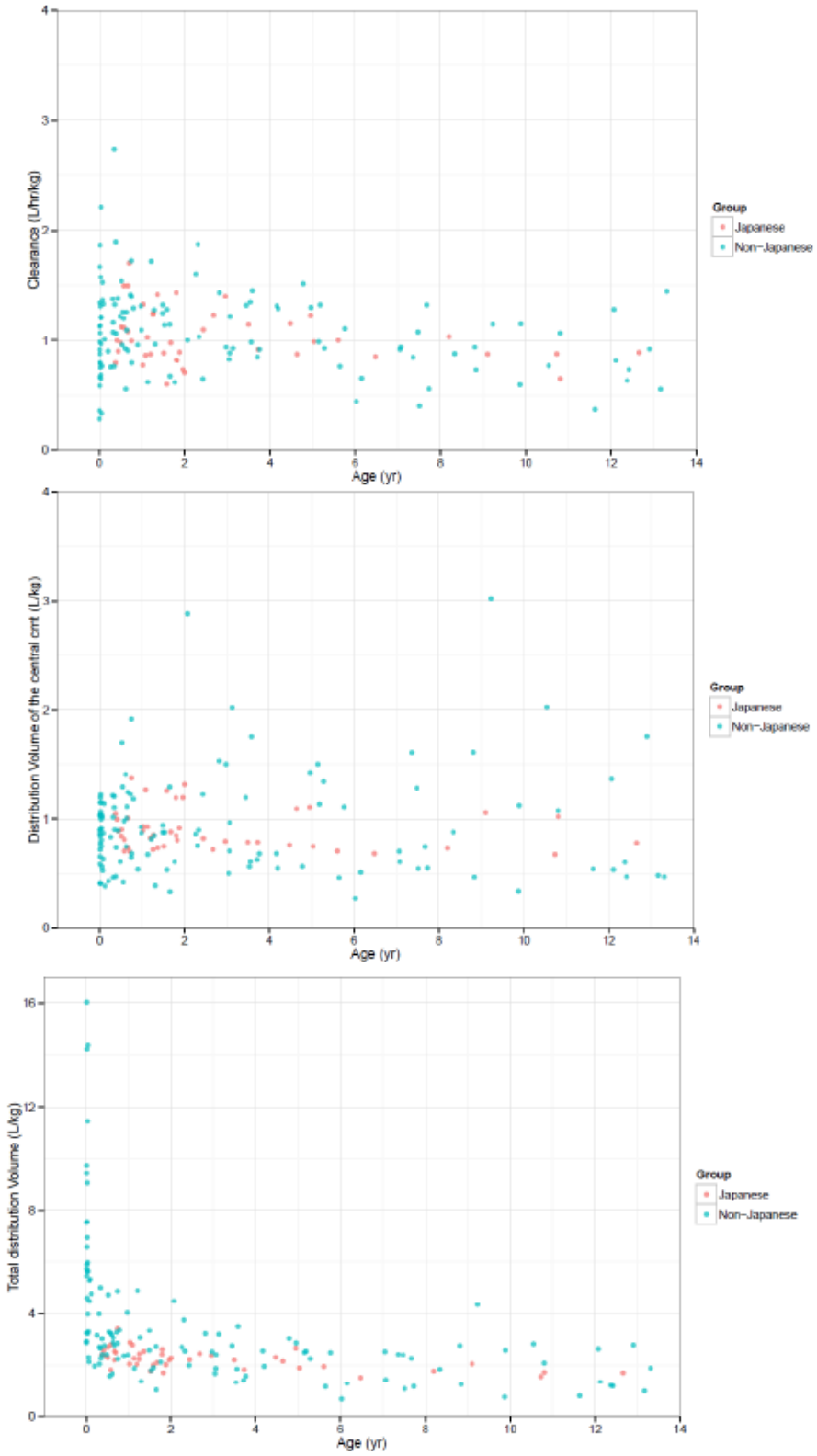
2.2 METHOD

A population PK evaluation of DEX infusion data for mechanically ventilated pediatric participants were performed for 4 global PK studies (Study DEX-09-08, the CHOP study, Study DEX-08-01, and Study DEX-11-01). There were a total of 1280 DEX concentration records from 124 pediatric participants (from 28 weeks gestational age to <17 years old) in this analysis.

In brief, a linear 2-compartment model was found to best characterize the pooled DEX concentration data collected from these pediatric participants for a range of DEX doses, which were administered as a short IV infusion, followed by a maintenance infusion of varying duration. Fixed allometric functions were used to account for the influence of body weight on all PK parameters in this pediatric population. The allometric exponent for DEX clearance was additionally adjusted in neonate participants. The intercompartmental clearance and the volume of the peripheral compartment for DEX were both found to be related to maturation, as described by age, according to a power function (both decrease with increasing age). The effects of ethnicity, sex, alanine aminotransferase, total bilirubin, heart physiology (single- vs double-ventricle), use of concomitant glucuronidation pathway inhibitors, albumin infusion, use of cardiopulmonary bypass, and site of sampling were not identified as statistically significant predictors of DEX PK variability. Clearance estimates from this model increase with increasing age and weight-adjusted clearance estimates decrease with increasing age, approaching values expected in adults. Volume of distribution estimates from this model increase with increasing age, and weight-adjusted volume of distribution estimates decrease with increasing age, approaching values expected in adults.

The model evaluation supports the robustness of the model to predict well over the entire range of concentrations. The reviewer concludes the analysis, and the corresponding conclusions and interpretations, presented by the applicant is reasonable (Clin Pharm Review dated 5/23/2013).

Figure 2 Comparison of CLw (Upper), Vc,w (Middle) and Vd,w (Lower) Between Japanese and Non-Japanese Pediatric Patients



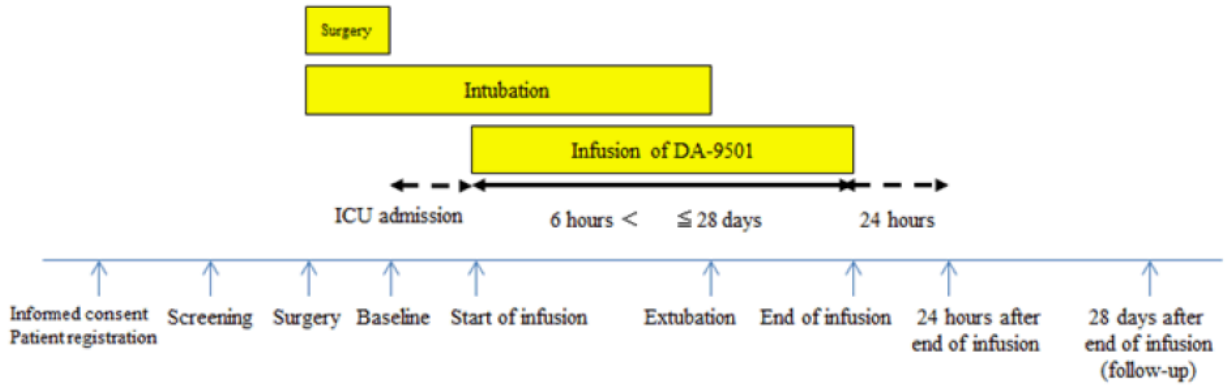
Source: PMAR EQDD-C080a-DP4-789 Report, Page 23, Figure 6

In this submission, a population PK evaluation of DEX infusion in Japanese pediatric participants in the ICU was conducted in Study C0801017 with a total of 308 DEX PK observations from 46 Japanese pediatric participants (from ≥45 weeks corrected gestational age to <17 years old). Participants were dosed with DEX via continuous infusion at different doses by age group for at least 6 hours in elective surgical participants and at least 24 hours in medical ICU participants for up to 28 days. In this population PK analysis, DEX concentration data collected from Japanese pediatric participants were applied to the final popPK model from the global studies to evaluate the performance of the established popPK model to predict DEX concentrations in Japanese pediatrics.

2.3 DATA

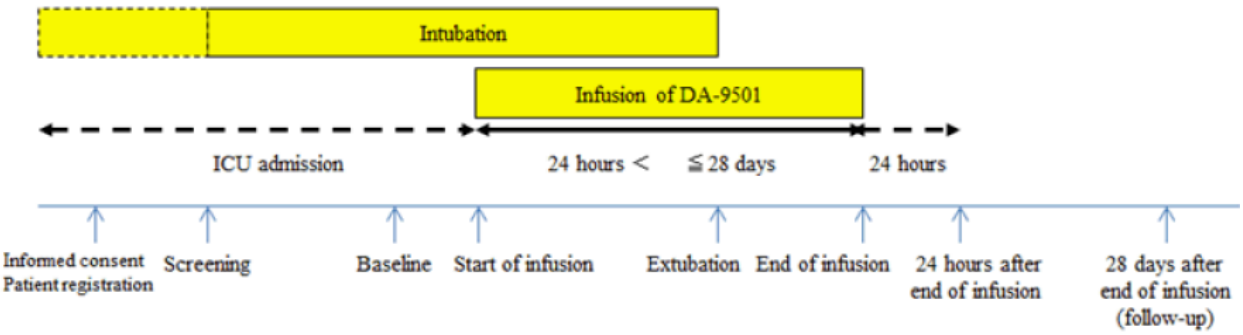
Study C0801017 was a Phase 3, multi-center, single-arm, open-label study with the objective of evaluating the efficacy, safety, and PK of dexmedetomidine (DA-9501) when given as continuous intravenous injection (IV) infusion in pediatric subjects ≥45 weeks corrected gestational age (CGA) to <17 years old. The study workflows for elective surgical subjects and medical ICU subjects are shown in Figure 3 and Figure 4, respectively.

Figure 3. Study Workflow for Elective Surgical Subjects



Source: PMAR EQDD-C080a-DP4-789 Report, Page 17, Figure 1

Figure 4. Study Workflow for Medical ICU Subjects



Source: PMAR EQDD-C080a-DP4-789 Report, Page 17, Figure 2

Total 308 dexmedetomidine PK observations from 46 Japanese pediatric patients were applied to our analysis. A listing of the baseline demographics for these subjects is given in **Table 2**.

Table 2: Summary of Baseline Demographics for the PopPK Analysis (n=46)

Subject Characteristic		Overall	≥45 wks CGA, <12 mos N = 11	≥12 mos, <24 mos N = 16	≥2 yrs, <6 yrs N = 11	≥6 yrs, <17 yrs N = 8
Age (year)	Mean (SD)	3.45 (3.86)	0.56 (0.13)	1.46 (0.33)	3.82 (1.20)	10.86 (2.89)
	Median	1.80	0.58	1.44	3.72	10.77
	Minimum, Maximum	0.38, 14.65	0.38, 0.75	1.02, 1.97	2.00, 5.61	6.48, 14.65
Weight (kg)	Mean (SD)	14.40 (11.47)	6.42 (1.15)	9.46 (1.65)	15.33 (3.07)	33.98 (15.14)
	Median	10.50	6.70	9.75	16.20	28.50
	Minimum, Maximum	4.50, 69.60	4.50, 8.30	6.20, 12.20	10.50, 19.50	22.30, 69.60
Sex (n, %)	Male	26 (56.5)	5 (45.5)	10 (62.5)	6 (54.5)	5 (62.5)
	Female	20 (43.5)	6 (54.5)	6 (37.5)	5 (45.5)	3 (37.5)

Source: PMAR EQDD-C080a-DP4-789 Report, Page 27, Table 6

The target numbers of subjects included in the efficacy/safety evaluation and in the PK evaluation by age group were shown in **Table 3**.

Table 3**: Target Number of Subjects and Dose by Age Group**

	Age group	Efficacy/safety evaluation: Target number of subjects	PK evaluation: Target number of subjectsa	Doseb
I	≥45 weeks CGA, <12 months	≥8	≥8	Maintenance initial dose: 0.2 µg/kg/h Maintenance dose range: 0.2 to 1.4 µg/kg/h
II	≥12 months, <24 months	≥16	≥8	
III	≥2 years, <6 years	≥16	≥8	
IV	≥6 years, <17 years	≥8	≥8	Maintenance initial dose: 0.2 µg/kg/h Maintenance dose range: 0.2 to 1.0 µg/kg/h
Target number of subjects		60	≥32	

a. Of enrolled subjects, those from whom informed consent for blood sampling for PK evaluation was obtained.
b. No initial loading dose was given in this study. Baseline body weight was be used to determine the dose of the investigational product.

Source: PMAR EQDD-C080a-DP4-789 Report, Page 18, Table 1

Exploratory PopPK Model Analysis

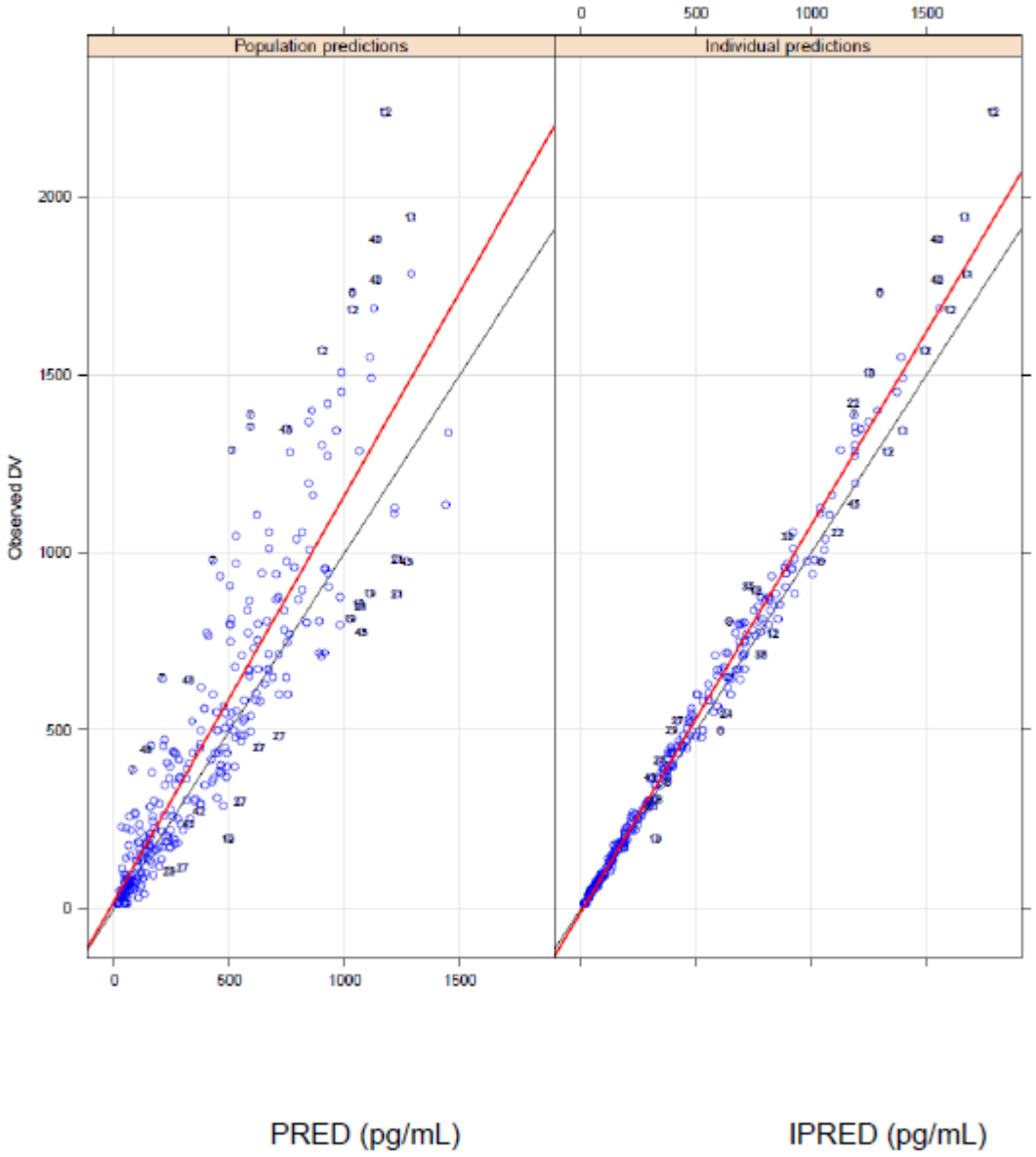
Japanese pediatric PopPK parameters were estimated based on the same structure of Cognigen PopPK model exploratively. Then, the Japanese pediatric PopPK parameters were compared with the original Cognigen's final model parameters, which were estimated using non-Japanese patients' data.

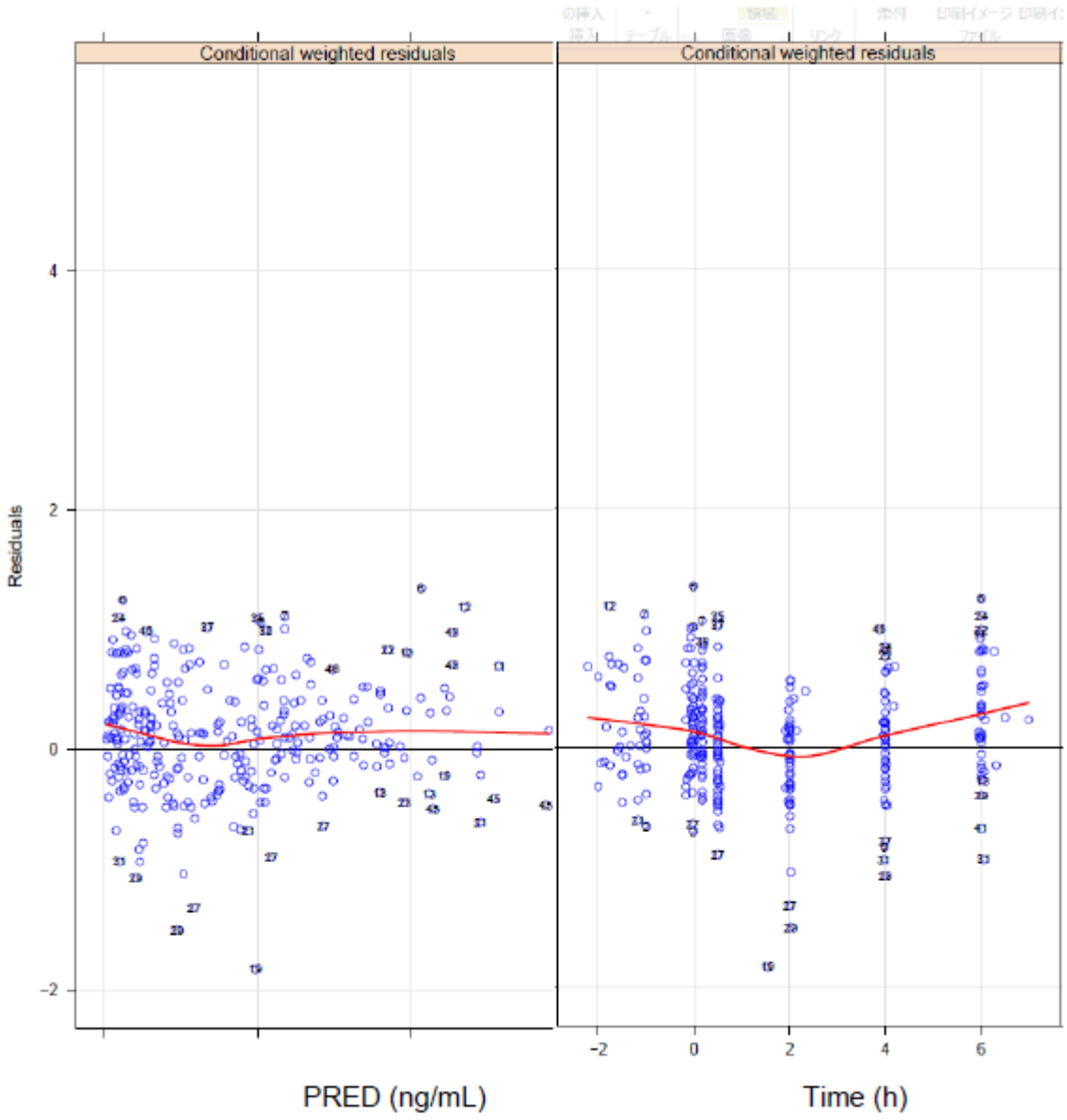
2.4 RESULTS

The validation of the final PopPK model was conducted using goodness of fit diagnostics (

Figure 5) and visual predictive check (Figure 6) to evaluate the performance of Cognigen PopPK model to predict DEX concentrations in Japanese pediatrics.

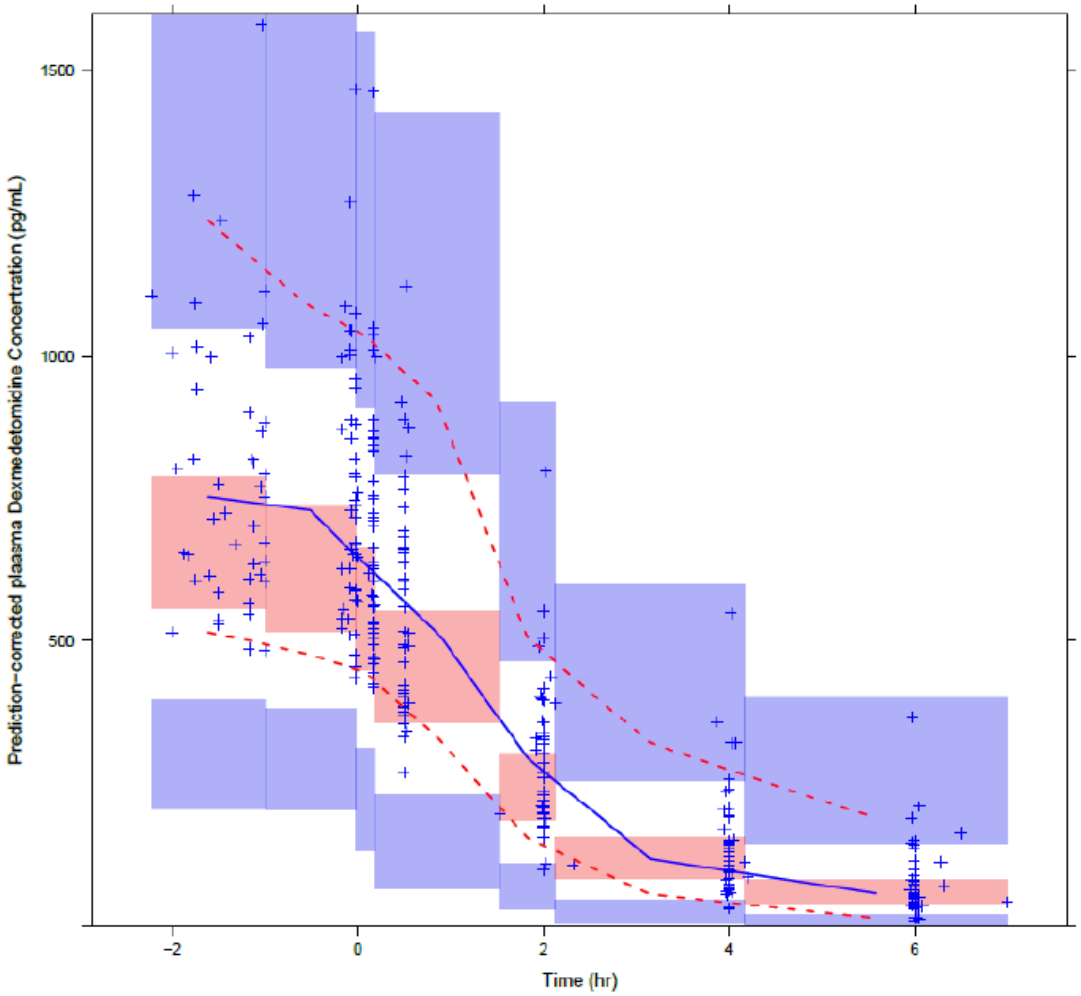
Figure 5: Diagnostic Plots for Plasma Dexmedetomidine Concentrations: Observations (DV) vs. PRED or IPRED (Left), CWRES vs. PRED or Time (Right)





Source: PMAR EQDD-C080a-DP4-789 Report, Page 30, Figure 5

Figure 6: Prediction-Corrected VPC Plots of Observed and Predicted Plasma Dexmedetomidine Concentrations vs. Time in Japanese Pediatric Patients



Source: PMAR EQDD-C080a-DP4-789 Report, Page 29, Figure 4

Estimated individual PK parameters in Japanese pediatric patients using the final population PK model from the global studies were within the range of those in non-Japanese pediatric patients, suggesting the PK similarity between these populations. The estimated mean PK parameters (CL, CLw, Vc and Vc,w) in **Table 4** and **Table 5** at relevant age groups are generally similar between Japanese and non-Japanese pediatric patients.

Table 4: Geometric Means Point Estimates and 95% Confidence Intervals of Pharmacokinetic Parameters by Pediatric Age Group (Global Studies: Study DEX-09-08, the CHOP Study, Study DEX-08-01, and Study DEX-11-01)

Age Group	CL (L/h)	CL_w (L/h/kg)	V_c (L)	$V_{c,w}$ (L/kg)
28 weeks GA - <1 month (N = 28)	2.28 (1.71, 3.05)	0.93 (0.76, 1.14)	2.03 (1.68. 2.46)	0.83 (0.72, 0.95)
1 month - <6 months (N = 14)	6.94 (5.46, 8.81)	1.21 (0.99, 1.48)	4.34 (3.25, 5.81)	0.76 (0.57, 1.00)
6 months - <12 months (N = 15)	8.15 (7.01, 9.47)	1.11 (0.94, 1.31)	7.29 (5.57, 9.53)	0.99 (0.75, 1.31)
12 months - <24 months (N = 13)	10.76 (9.09, 12.74)	1.06 (0.87, 1.29)	7.35 (5.59, 9.67)	0.72 (0.55, 0.95)
2 years - <6 years (N = 26)	15.89 (14.00, 18.04)	1.11 (1.00, 1.23)	13.78 (10.66, 17.83)	0.96 (0.76, 1.21)
6 years - <17 years (N = 28)	24.45 (19.34, 30.92)	0.80 (0.69, 0.92)	24.47 (17.06, 35.10)	0.80 (0.61, 1.04)

Source: Cognigen Population PK Report, Page 62-63, Table 13-14

Table 5: Geometric Means Point Estimates and 95% Confidence Intervals of Pharmacokinetic Parameters[a] by Pediatric Age Group (Japanese Study: Study C0801017)

Age Group	Geometric Mean (95% CI) [relative 95% CI][b]			
	CL (L/h)	CL_w (L/h/kg)	V_c (L)	$V_{c,w}$ (L/kg)
Age Group I 45 weeks CGA to <12 months (N = 11)	7.09 (5.54, 9.06) [0.78, 1.28]	1.12 (0.88, 1.43) [0.78, 1.28]	5.65 (4.78, 6.67) [0.85, 1.18]	0.89 (0.76, 1.06) [0.85, 1.18]
Age Group II 12 months - <24 months (N = 16)	8.98 (7.48, 10.78) [0.83, 1.20]	0.96 (0.80, 1.16) [0.83, 1.20]	8.58 (7.48, 9.84) [0.87, 1.15]	0.92 (0.80, 1.06) [0.87, 1.15]
Age Group III 2 years - <6 years (N = 11)	15.76 (12.94, 19.20) [0.82, 1.22]	1.05 (0.86, 1.28) [0.82, 1.22]	12.90 (10.89, 15.28) [0.84, 1.18]	0.86 (0.72, 1.02) [0.84, 1.18]
Age Group IV 6 years - <17 years (N = 8)	26.20 (20.64, 33.25) [0.79, 1.27]	0.82 (0.65, 1.04) [0.79, 1.27]	27.47 (19.34, 39.01) [0.70, 1.42]	0.86 (0.61, 1.22) [0.70, 1.42]

a Individual parameters estimated using the final population PK model from the global studies
b 95% CI divided by geometric mean
Source: PMAR EQDD-C080a-DP4-789 Report, Page 30, Table 19

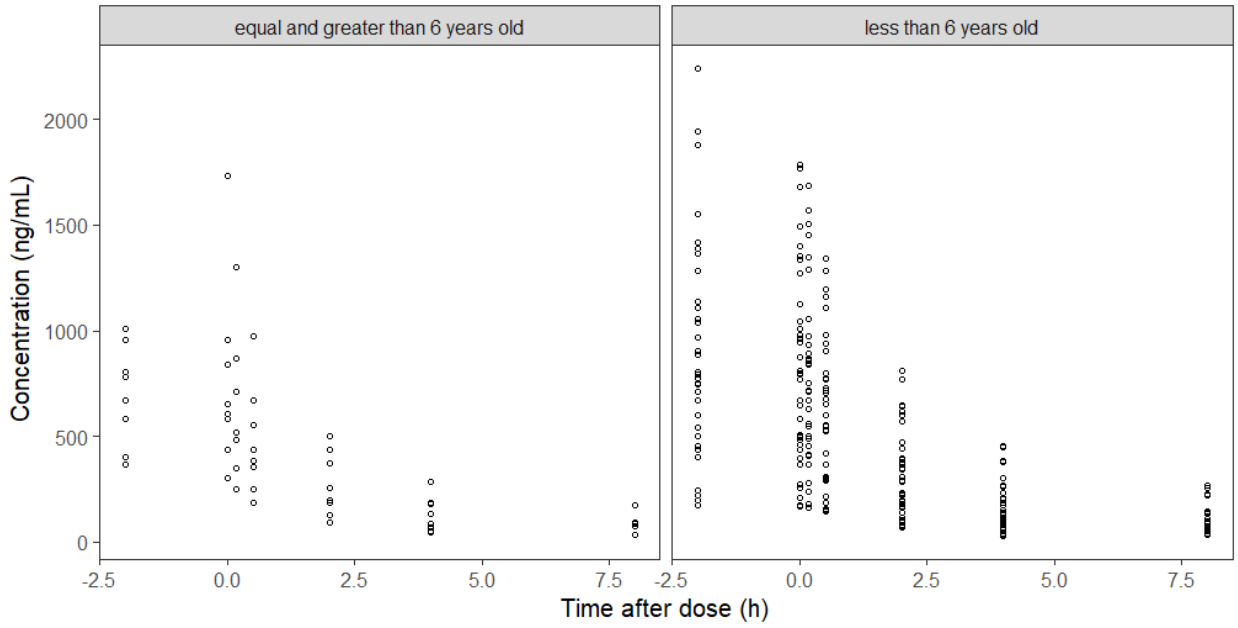
3. REVIEWER'S ANALYSIS

The reviewer was able to reproduce the applicant's PopPK results with NONMEM (version:7.4.3). No additional modeling analysis was conducted.

3.1 Overview of Observed Data

Figure 7 presents PK data of DEX in Japanese patients from different age groups.

Figure 7: Observed Plasma Dexmedetomidine Concentrations vs. Time by Age Groups

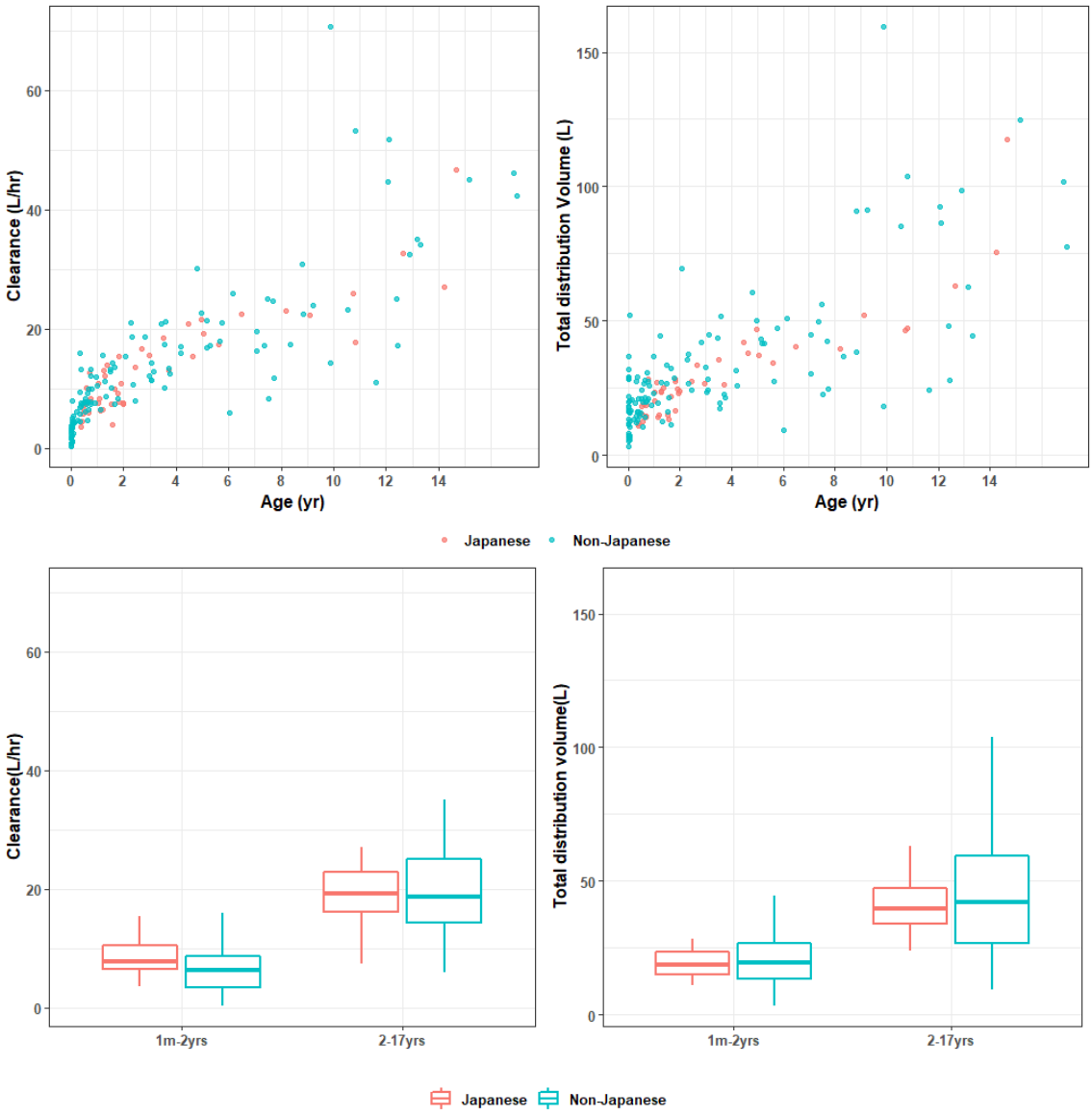


Source: Reviewer's analysis

3.2 Comparison of PK Parameters between Japanese and Non-Japanese Pediatric Patients

Japanese pediatric PopPK parameters were estimated based on the same structure of Cognigen PopPK model exploratively. Estimated individual PK parameters in Japanese pediatric patients were within the range of those in non-Japanese pediatric patients, suggesting the PK similarity between these populations (**Figure 8**).

Figure 8: Comparison of Clearance and Volume of Distribution Between Japanese and Non-Japanese Pediatric Patients



Source: Reviewer's analysis

Reviewer's Comments:

Overall, popPK model from the global studies is appropriate to describe DEX PK in Japanese pediatric participants. Estimated individual PK parameters in Japanese pediatric patients using the final population PK model from the global studies were within the range of those in non-Japanese pediatric patients, suggesting the PK similarity between these populations.

LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	Description	Location
PK data or population analysis	Exploratory PK and popPK analysis	\\Review\\2022\\NDA 021038 S028 Dexmeditomidine HCl\\PopPK\\Reviewer\\Rscript

PROPOSED LABELING CHANGES

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Applicant's proposal

Section 12.3 Pharmacokinetics

Table 10: Geometric Mean Point Estimates and 95% Confidence Intervals of PK Parameters by Pediatric Age Group

Age Group	N	CL (L/h/kg)	Vc (L/kg)
Under 1 month	28	0.93 (0.76, 1.14)	0.83 (0.72, 0.95)
1 to less than 6 months	14	1.21 (0.99, 1.48)	0.76 (0.57, 1.00)
6 to less than 12 months	15	1.11 (0.94, 1.31)	0.99 (0.75, 1.31)
12 to less than 24 months	13	1.06 (0.87, 1.29)	0.72 (0.55, 0.95)
2 to less than 6 years	26	1.11 (1.00, 1.23)	0.96 (0.76, 1.21)
6 to less than 17 years	28	0.80 (0.69, 0.92)	0.80 (0.61, 1.04)

Abbreviations: CL = plasma clearance, Vc = volume of the central compartment.

Reviewer's Recommendation (Refer to Clin Pharm Review Dated 5/23/2013)

Table 10: Geometric Mean Point Estimates and 95% Confidence Intervals of PK Parameters by Pediatric Age Group

Age Group	N	CL (L/h)	Vc (L)
~~Under 1 month~~	~~28~~	~~0.93 (0.76, 1.14)~~	~~0.83 (0.72, 0.95)~~
1 to less than 6 months	14	~~1.21 (0.99, 1.48)~~ 6.94 (5.46, 8.81)	~~0.76 (0.57, 1.00)~~ 4.34 (3.25, 5.81)
6 to less than 12 months	15	~~1.11 (0.94, 1.31)~~ 8.15 (7.01, 9.47)	~~0.99 (0.75, 1.31)~~ 7.29 (5.57, 9.53)
12 to less than 24 months	13	~~1.06 (0.87, 1.29)~~ 10.76 (9.09, 12.74)	~~0.72 (0.55, 0.95)~~ 7.35 (5.59, 9.67)
2 to less than 6 years	26	~~1.11 (1.00, 1.23)~~ 15.89 (14.00, 18.04)	~~0.96 (0.76, 1.21)~~ 13.78 (10.66, 17.83)
6 to less than 17 years	28	~~0.80 (0.69, 0.92)~~ 24.45 (19.34, 30.92)	~~0.80 (0.61, 1.04)~~ 24.47 (17.06, 35.10)

Abbreviations: CL = plasma clearance, Vc = volume of the central compartment.

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/s/

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