CLINICAL PHARMACOLOGY REVIEW

NDA: 21-038 S21 S22	Submission Date(s): 12/17/2012
Brand Name	Precedex
Generic Name	Dexmedetomidine HCl
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Pharmacometrics Reviewer	Satjit Brar, Pharm.D. Ph.D.
Pharmacometrics Team Leader	Atul V. Bhattaram, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia and Analgesia Products
Sponsor	Hospira Inc
Relevant IND(s)	32,934
Submission Type	Pediatric Submission
Formulation; Strength(s)	IV injection;
Indication	ICU sedation of initially intubated mechanically ventilated patients
Proposed Dosage Regimen	Approved Adults: 1 mcg/kg 10 min bolus infusion followed by 0.2 – 0.7 mcg/kg/hr infusion
	(b) (4)
	(b) (4)

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1 Executive Summary

1.1 Recommendation

The submission is acceptable from a clinical pharmacology perspective, provided that a mutually acceptable labeling is agreed by the sponsor.

1.2 Phase IV Commitments

None.

1.3 Clinical Pharmacology Findings

Hospira Inc. submitted a pediatric (b) (4) supplement to the New Drug Application (NDA 21-038) on 12/17/2012. The pediatric clinical studies and trials were executed to fulfill the requirements of the Agency issued Pediatric Written Request (Final Amendment dated 8/30/2011). Precedex is approved for adult ICU sedation and procedural sedation.

Dexmedetomidine, also referred in certain sections as DEX, is intended for sedation and analgesia in an intensive care setting Unit (ICU) and is claimed to produce titratable, predictable sedation, from which patients are easily arousable and cooperative. Data from previously reviewed (original NDA 21-038, review in darrts on) adult study Dex-97-028, a dose ranging study, indicates concentrations above 0.3 ng/mL may be effective in producing Ramsay Sedation Scale (RSS) of >3 (acceptable level of sedation).

With regard to the current submission pertaining to pediatric patients requiring sedation in ICU setting, five clinical studies with pediatric clinical PK and PD information were submitted:

1. Study W98-266 was a Phase I, multi-center, open-label study conducted by Abbott Laboratories evaluating the pharmacokinetics (PK) and pharmacodynamics (PD) of DEX in pediatric patients aged 2 to 12 years undergoing surgeries requiring general or general and epidural anesthesia and an overnight stay in the hospital in a monitored setting. (Note: This study was not part of the PWR and it was initiated and completed before 2001)

The following four studies were conducted to fulfill the requirements of the pediatric written request issued by the Agency.

2. The CHOP (Children's Hospital of Philadelphia) Study was a physician sponsored Phase I, single center, dose escalation PK and PD study of a single loading dose of DEX followed by a continuous infusion for up to 24 hours in infants aged 1 month to 2 years of age.

3. Study DEX-11-01 was a Phase II, open-label, single center, pharmacokinetic and pharmacodynamic study of DEX in pediatric subjects aged 12 months through < 24 months old, with DEX administered as an IV loading dose followed by a continuous IV infusion. This study was conducted to complete population requirements not met by CHOP.

4. Study DEX-08-01 was a Phase II, open-label, multicenter, escalating dose study to determine the pharmacokinetic and pharmacodynamic profile of DEX in pediatric subjects ages ≥2 through <17 years old, when DEX was administered as an intravenous (IV) loading dose followed by a continuous IV infusion.

5. Study DEX-09-08 was a Phase II/III, open-label, multicenter, safety, efficacy and pharmacokinetic study of DEX administered as an IV loading dose followed by a continuous IV infusion in neonates ≥ 28 weeks to ≤ 44 weeks gestational age who were initially intubated and mechanically ventilated.

The sedative effects of dexmedetomidine in adults have been described previously to set the basic understanding of the clinical pharmacology of dexmedetomidine as it relates to its clinical use. From a developmental stand point, it is reasonable to assume that physiological development and pharmacological response to drugs and pharmacokinetic disposition of drugs mature with age. The review will focus on sedative effects produced by dexmedetomidine in older pediatric age groups (2 to 6 yrs, >6 to 17 yrs age) followed by infants (1 month to 2 years) and, neonates (term and pre-term).

According to the sponsor, the PK/PD studies served as the basis for dose-selection in pediatric efficacy trial DEX-08-05. The pediatric efficacy clinical trial is the subject of medical officer review and it has been briefly described in the pharmacometrics review Section 4.1.1.

Pharmacokinetics and Pharmacodynamics of dexmedetomidine for each of the studies conducted in different age groups will be described in summary below.

Collective pharmacokinetic data from all pediatric safety, PK, PD studies were analyzed employing population pharmacokinetic analysis methodology. Dr. Satjit Brar analyzed the population PK analysis submitted by the sponsor. Additionally, Dr. Brar also explored concentration-response analysis of dexmedetomidine to sedation endpoints in his review. Pharmacometrics review by Dr. Satjit Brar is appended to the clinical pharmacology review (See appendix 4.2).

Conclusions of Clinical Pharmacology Review (including Pharmacometric review of population PK and systemic exposure-response analysis):

1. The PK of DEX has been characterized, with adequate precision, for different pediatric age groups from 28 weeks gestational age to <17 years. A population PK model was generated from PK information that included rich sampling data available from four PK studies performed in a patient population of n=131 subjects. Various loading and maintenance doses, in the studies described above, were employed to assess the PK of DEX in the pediatric population.

2. Clearance and volume of distribution increased with increasing age and values of weight-adjusted clearance decreased with increasing age, approaching

values expected in adults (See table below, excerpted from pharmacometrics review Table 9). In comparison, clearance of dexmedetomidine is 39 L/hr (approximately 0.58 L/hr/kg for a 70 kg patient) in adults (as indicated in the current Precedex product label). (b) (4)

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

Age Group	CL (L/hr)	CLw (L/hr/kg)	Vc (L)	Vcw (L/kg)
28 wks GA to < 1 mo (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 mo to < 6 mos (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 mos to < 12 mos (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 mos to < 24 mos (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 yrs to < 6 yrs (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 yrs to ≤ 16 yrs (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)

Abbreviations: CL = clearance; CLw = weight-adjusted clearance; GA = gestational age; hr = hour; kg = kilogram; L = liter; mo(s) = month(s); N = number of subjects in each Age Group; Vc = volume of central compartment; Vcw = weight-adjusted volume of central compartment; wks = weeks; yrs = years

The observed average dose-normalized steady-state plasma concentrations following 1 mcg/kg 10 min 0.7 mcg/kg/h dose are tabulated from DEX-08-01 and CHOP studies.

Age Group	Css (pg/mL)
1 to <6 months	606
6 to < 12 months	719
12 to 24 months	696
2 to <6 yrs	789
>=6 to 17 yrs	1203
Adult (From Label)	1370

Clinical trial DEX-08-05 employed loading doses that are half as much as approved adult doses.

Table. Dosing scheme for Study DEX-08-05

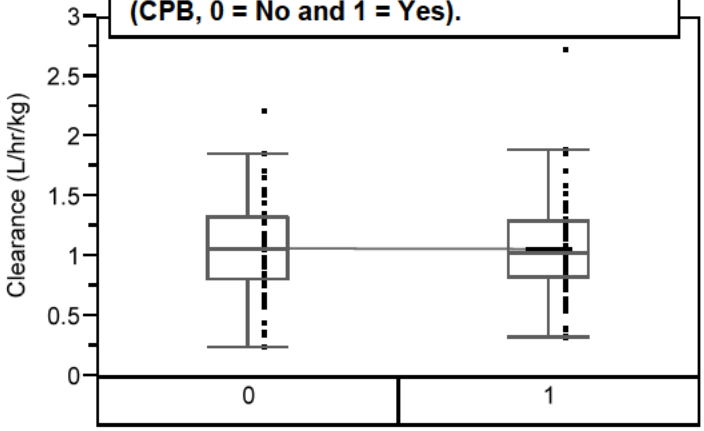
	Treatment Groups	
	Dose Level 1	**Dose Level 2**
S/P Cardiopulmonary Bypass	LD*: 0.2 mcg/kg MD: 0.025-0.5 mcg/kg/hr	LD*: 0.5 mcg/hr MD: 0.1-0.7 mcg/kg/hr
All other diagnoses	LD*: 0.3 mcg/kg MD: 0.05-0.5 mcg/kg/hr	LD*: 0.6 mcg/kg MD: 0.2-1.4 mcg/kg/hr

*Loading dose was optional.
Abbreviations: CSR = clinical study report; DEX = dexmedetomidine; hr = hour; kg = kilogram; LD = loading dose (administered over 10-20 minutes); mcg = microgram; MD = maintenance dose (titration range); S/P = status-post.
Source: DEX-08-05 CSR, Figure 2.

Based on approved label, Precedex is generally initiated with a loading dose of 1 mcg/kg over 10 min infusion, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr in adult. In study DEX-08-01, when the pediatric patients was given a loading dose of 1 mcg/kg over 10 minutes infusion followed by a maintenance infusion of 0.7 mcg/kg/hr (Dose level 3), the mean Css is 1347 pg/mL, comparable to the Css of 1370 pg/mL in adults. In study DEX08-05, the loading dosing in the high dose group (Dose level 2) is 0.5-0.6 mcg/hr, and the maintenance dose has a wide range starting from as low as 0.1-0.2 mcg/kg/hr. Since the PK of DEX is dose-proportional, it is reasonable to think that the systemic exposure (Cmax, AUC, Css) in high dose group in DEX-08-5 will be lower compared to approved adult dose. However, safety of adult dosing regimen in pediatric population is not fully known.

3. Several pediatric patients received different dosing based on requirement of cardiopulmonary bypass (CPB) surgery or other types of surgeries. Population PK analysis employed CPB as one of the covariates to test its influence on dexmedetomidine clearance and volume based on physiological plausibility. However, no effect met the pre-specified criteria for inclusion in the population PK model. The adjacent plot (figure 2 described in the attached pharmacometrics review is excerpted) depicts the weight-adjusted clearance as a function of CPB. The pharmacometrics reviewer indicates that Patients who underwent CPB had an average body-weight adjusted clearance of 1.07 (95% CI 1.04 – 1.11) L/hr/kg, while and patients who did not have the procedure had an average body-weight adjusted

Figure: Weight-adjusted clearance as a function of Cardio-Pulmonary Bypass (CPB, 0 = No and 1 = Yes).



clearance of 1.1 (95% CI 1.05 – 1.13) L/hr/kg (p-value >0.05). This result is in contrast to a previously developed 2-compartment population PK model of dexmedetomidine in infants (aged 1 to 24 months) after open heart surgery.* In this published model, significant covariate effects included total bypass time on clearance. The data available for covariate assessment differed from Su et al., where total bypass time was determined to be a significant covariate as a continuous variable. The current analysis was limited to evaluation of CPB use as a dichotomous variable indicating occurrence or lack of occurrence. (*Su F, Nicolson SC, Gastonguay MR, et al. Population pharmacokinetics of dexmedetomidine in infants after open heart surgery. Anesth Analg. 2010; 110:1383-1392.)

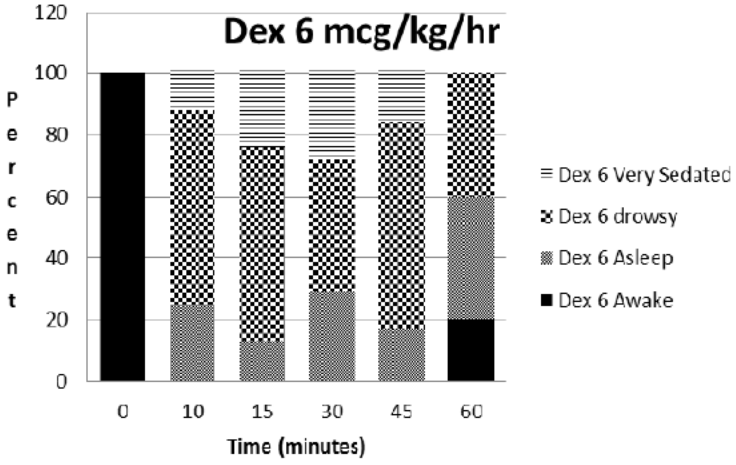
4. Pediatric studies W98-266, DEX-08-01, CHOP study had significant evaluation of sedative and cardiovascular effects of dexmedetomidine. In general, sedative effects were noted in the supportive open-label clinical pharmacology studies. Additionally, the studies also show the expected hypotensive and bradycardic effects of dexmedetomidine in a dose-dependent manner.

5. Use of different sedation scales across different studies did not allow for a meta-analysis of sedative effects of different doses of dexmedetomidine employed in the clinical pharmacology studies. Although exposure-response relationships for dexmedetomidine showed a trend with respect to sedation scales, the analysis was confounded by the concomitant use of midazolam in Study DEX-08-01. Patients that achieved the highest dexmedetomidine concentrations, and largest effects on sedation, also had larger doses of midazolam compared to those patients with lower dexmedetomidine concentrations and lower sedative effect. For this reason, the analysis was inconclusive in determining whether the dosing regimen is supported by the exposure-response relationship.

1. Summary of Study W98-266 in pediatric patients aged 2 – 12 years age.

Study W98-266 was a Phase I, multi-center, open-label study conducted by Abbott Laboratories evaluating the pharmacokinetics (PK) and pharmacodynamics (PD) of DEX in pediatric patients aged 2 to 12 years undergoing surgeries requiring general or general and epidural anesthesia and an overnight stay in the hospital in a monitored setting. In this study, pediatric patients received Dexmedetomidine as an IV infusion for 10 minutes of 2 mcg/kg/hr for Group I, 4 mcg/kg/hr for Group II, and 6 mcg/kg/hr in Group III. For each of the above treatment groups, a separate control group of up to 4 subjects was recruited where the pediatric patient received comparable anesthetic procedure. (b) (4) the study results indicate that following use of approved adult loading dose (1 mcg/kg 10 minute infusion or 6 mcg/kg/hr infused for 10 minutes), pediatric patients experience significant sedation (See figure below).

Figure: Percent of pediatric patients (2 -17 yrs) that experienced pharmacodynamic effects of dexmedetomidine (asleep, drowsy or very sedated) following loading infusion of (1 mcg/kg 10 minute infusion or 6 mcg/kg/hr infused for 10 minutes) over time.



PK parameters of dexmedetomidine following the loading dose infusion were dose-proportional.

Figure: Mean dexmedetomidine PK profile over time following loading infusion

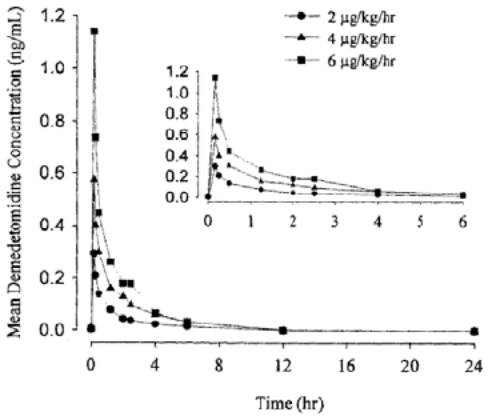


Table: Mean (SD) Pharmacokinetic Parameters of dexmedetomidine following loading infusion.

Pharmacokinetic Parameters	2.0 µg/kg/h Dose Group	4.0 µg/kg/h Dose Group	6.0 µg/kg/h Dose Group
	7	8	8
C_{max} (ng/mL)	0.298 ± 0.168	0.623 ± 0.312	1.150 ± 0.633
AUC_{∞} (ng•h/mL)	0.395± 0.102	0.895 ± 0.312	1.262 ± 0.365
$t_{½}$ (h)‡	2.18 ± 0.46	2.12 ± 0.77	1.61 ± 0.28
V_{SS} (L)	38.3 ± 7.9	42.9 ± 13.3	34.8 ± 8.5
V_{SS} (L/kg)	2.33 ± 0.57	2.13 ± 0.32	1.65 ± 0.43
CL (L/h)	14.5 ± 1.6	16.1 ± 4.2	18.3 ± 5.4
CL (L/h/kg)	0.894 ± 0.231	0.835 ± 0.296	0.848 ± 0.223
T_{max} (h)	0.186 ± 0.045	0.223 ± 0.116	0.187 ± 0.040

Note: 6 mcg/kg/hr infusion rate is equal to 1 mcg/kg over 10 minutes.

Safety conclusions from study W98-266:

A classical pharmacological effect of alpha2-adrenergic receptor agonists, such as dexmedetomidine, is hypotension and bradycardia. In this particular study W98-266, patients exhibited dose-related increase in hypotension and bradycardia. The systolic and diastolic blood pressure as well as heart rate decreased with dose for at least 1 hour after the infusion of dexmedetomidine.

		Group I		Group II		Group III	
		Control Mean (SE)	Dex 2 mcg/kg/hr Mean (SE)	Control Mean (SE)	Dex 4 mcg/kg/hr Mean (SE)	Control Mean (SE)	Dex 6 mcg/kg/hr Mean (SE)
Pre-infusion Baseline		N=4	N=8	N=4	N=7	N=3	N=8
	SBP	112.0 (1.5)	104.4 (4.4)	95.0 (6.3)	105.1 (3.8)	108.7 (10.5)	115.4 (1.9)
	DBP	66.3 (6.2)	59.3 (3.8)	52.0 (7.4)	59.4 (2.4)	62.3 (5.2)	69.3 (2.3)
	Pulse	85.3 (13.6)	103.5 (6.6)	89.3 (6.3)	97.4 (7.6)	109.3 (17.6)	98.5 (4.6)
10 minutes		N=4	N=8	N=4	N=7	N=3	N=8
	SBP	-1.0 (3.1)	0.8 (2.8)	8.8 (5.0)	-2.9 (4.7)	11.7 (14.2)	-5.1 (2.0)
	DBP	-2.0 (4.2)	-0.3 (4.1)	15.3 (12.0)	3.9 (3.6)	8.0 (3.1)	-4.9 (3.7)
	Pulse	3.0 (2.0)	-3.0 (4.7)	-2.8 (3.6)	-5.1 (6.0)	6.0 (5.3)	-23.6 (5.1)
15 minutes		N=4	N=8	N=4	N=7	N=2	N=8
	SBP	-1.0 (5.4)	-1.4 (2.6)	2.5 (2.8)	-3.3 (6.1)	6.0 (22.0)	-9.9 (2.7)
	DBP	-0.3 (3.4)	3.3 (6.6)	5.3 (5.3)	0.9 (2.5)	0.0 (6.0)	-10.5 (2.7)
	Pulse	3.0 (2.0)	-5.6 (5.7)	6.5 (3.1)	-3.3 (3.6)	4.0 (13.9)	-20.8 (5.4)
30 minutes		N=4	N=8	N=4	N=7	N=4	N=8
	SBP	-6.0 (6.2)	-6.5 (3.2)	3.3 (5.3)	-8.7 (4.7)	3.5 (10.5)	-14.3 (2.8)
	DBP	-1.5 (4.6)	-2.6 (2.6)	-0.3 (8.7)	-4.0 (3.3)	3.3 (6.5)	-13.5 (4.4)
	Pulse	5.8 (3.0)	-8.1 (4.9)	15.5 (11.5)	-16.8 (4.2)	22.5 (18.5)	-20.0 (4.8)
45 minutes		N=4	N=8	N=3	N=5	N=4	N=8
	SBP	-0.8 (4.5)	-5.4 (3.7)	-4.0 (4.4)	-14.4 (7.7)	0.3 (8.0)	-22.4 (3.1)
	DBP	0.8 (5.8)	-3.1 (3.3)	-2.0 (13.3)	-8.4 (5.1)	-0.3 (6.1)	-19.1 (5.1)
	Pulse	0.5 (5.4)	-5.1 (4.4)	12.0 (10.4)	-17.6 (4.1)	13.0 (14.4)	-17.4 (4.8)
1 hour		N=3	N=7	N=3	N=6	N=4	N=8
	SBP	3.7 (5.2)	-7.3 (6.1)	1.3 (9.2)	-11.2 (5.8)	-4.5 (8.6)	-24.5 (3.6)
	DBP	7.7 (10.1)	-1.8 (6.1)	-0.3 (13.6)	-11.7 (4.2)	-0.5 (6.3)	-26.4 (3.3)
	Pulse	-2.3 (5.8)	0.1 (4.2)	5.0 (6.1)	-9.1 (7.1)	10.8 (8.9)	-17.8 (4.4)

Note: Sample sizes are from number of [illegible] systolic blood pressure measurements.
Cross-reference: Table 14.2__2.3 and Appendix 16.2__9.1.

Table: Mean Change in Vital signs from Baseline Up to One hour Post Study Drug Infusion.

The study investigator's later published their findings in a peer reviewed journal Anesthesiology in 2006(105:1098-110). The author's described that the pharmacokinetics of dexmedetomidine were predictable and that the hemodynamic responses decreased with increasing doses of dexmedetomidine. They note that the hypotensive effects of dexmedetomidine were significant but reversible as noted in the adjacent figure.

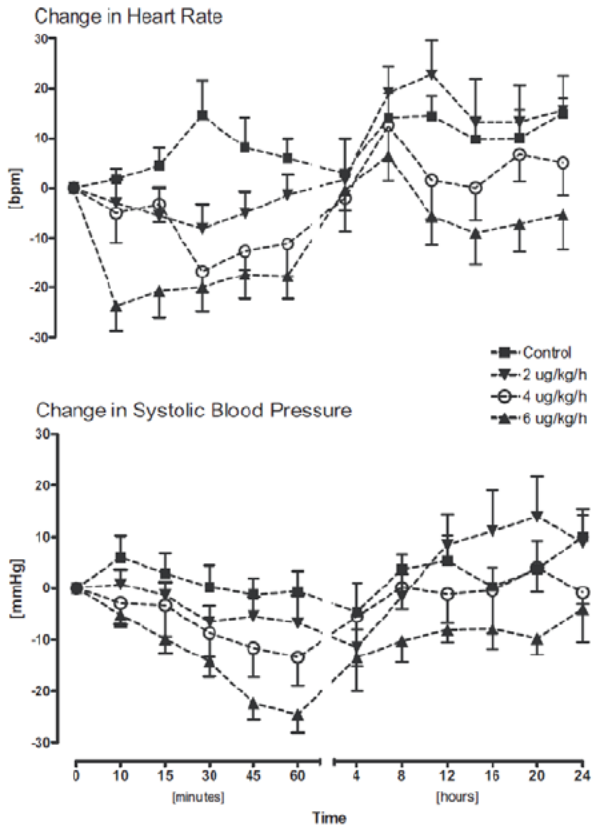


Figure: Mean (− SD) change in heart rate (top) and systolic blood pressure (bottom) from baseline (before dexmedetomidine infusion) for the four doses: control (0 mcg/kg/hr) and infusions of 2, 4, and 6 mcg/kg/hr dexmedetomidine (for 10 min) (corresponding to 0.33, 0.66, and 1.0 g/kg) recorded for 24 h.

2. Summary of Study DEX-08-01 (Phase II, open-label, multicenter, escalating dose).

This study was conducted to determine the pharmacokinetic and pharmacodynamic profile of DEX in pediatric patients ages ≥2 through <17 years old, when DEX was administered as an intravenous (IV) loading dose followed by a continuous IV infusion. The recruited pediatric patients were initially intubated mechanically ventilated and required sedation in the pediatric intensive care unit (PICU).

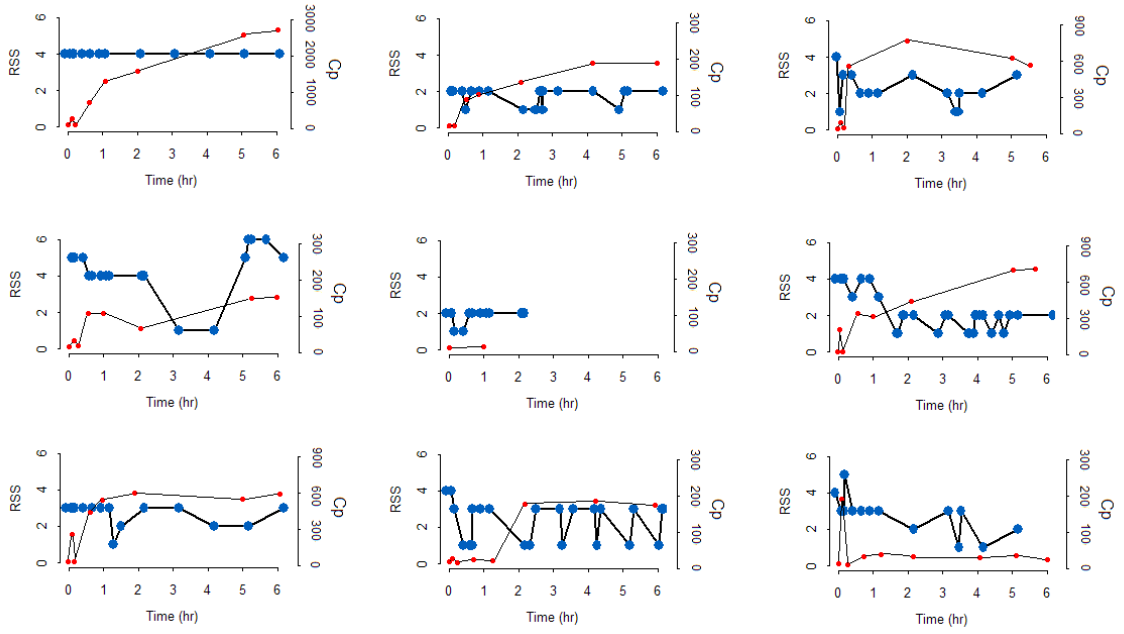
Table: The sponsor evaluated the following loading and maintenance dose of dexmedetomidine.

Age Group I (Ages ≥ 2 through <6 years old) Age Group II (Ages ≥ 6 through <17 years old)	DEX Loading Dose (10 minutes)	DEX Maintenance Infusion (at least 6 hours and up to 24 hours)	Post-Treatment Period
Dose Level 1	0.25 mcg/kg	0.2 mcg/kg/hr	24 hours
Dose Level 2	0.50 mcg/kg	0.4 mcg/kg/hr	24 hours
Dose Level 3	1.00 mcg/kg	0.7 mcg/kg/hr	24 hours
Dose Level 4	1.00 mcg/kg	2.0 mcg/kg/hr	24 hours
Abbreviations: hr = hour; kg = kilogram; mcg = microgram.			

It is noteworthy that the adult approved dosing regimen (Dose Level 3) was employed in this particular study.

From a PK perspective, the disposition of dexmedetomidine exhibited dose-proportionality with regard to typical exposure parameters (Cmax, AUC, Css) following different dose levels.

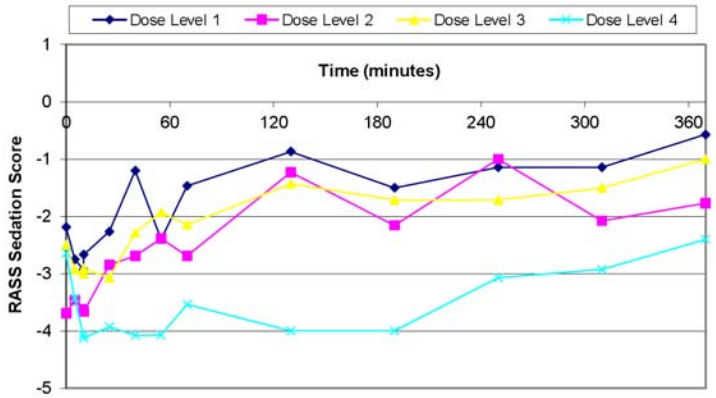
Figure. Individual plots of concentration (small red dots) and RSS (large blue dots) as a function of time for Study DEX-08-01. Excerpted from Pharmacometrics Review Figure 10.



Excerpt from Pharmacometrics review: Although exposure-response relationships for DEX showed a trend with respect to sedation scales, the analysis was confounded by the concomitant use of midazolam in Study DEX-08-01. Patients that achieved the highest DEX concentrations, and largest effects on sedation, also had larger doses of midazolam compared to those patients with lower DEX concentrations and lower sedative effect. For this reason, the analysis was inconclusive in determining whether the dosing regimen is supported by the exposure-response relationship.

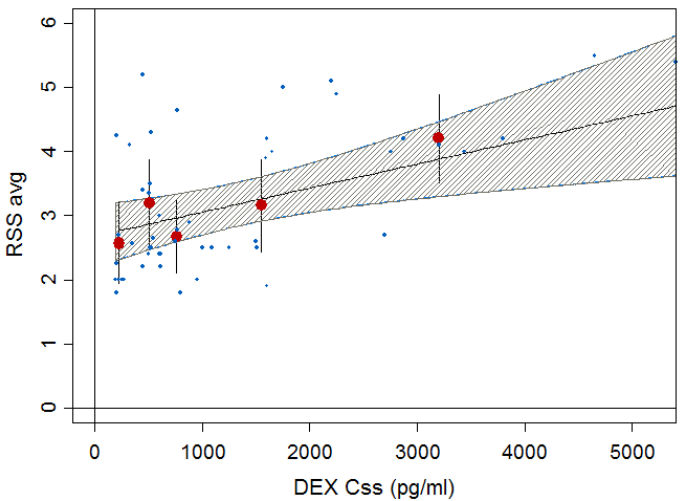
Pharmacodynamics of dexmedetomidine in 2 – 17 yr old patients:

Figure: Mean RASS (Richmond Agitation and Sedation Scale) profile following different doses of dexmedetomidine during the first 6 hours in Study DEX-08-01



Upon closer examination, pharmacometrics reviewer noted the following: For RASSavg, an exposure-response relationship was not observed using a linear model (Figure 3 of Pharmacometrics review attached). Regardless of steady state DEX concentration, an increase in effect (decrease of RASS scale) was not observed. On the other hand, the analysis of RSSavg as result yielded a positive relationship with DEX concentration (p-value <0.05 for slope of the linear relationship). With an increase in DEX steady state concentrations, increased sedation (i.e., increase in RSSavg) was observed (Figure 4 of the pharmacometrics review attached, also see below). It is important to note that the observed relationship is driven by the observations within the far-right quantile (at concentrations >2500 pg/ml). Below these concentrations, the quantile binned data suggests no relationship.

Figure: Individual Average Ramsay Sedation Scale, RSS (from 0-6 hours), as a function of steady state DEX concentration from Study DEX-08-01. A total of n=50 pediatric subjects informed the analysis (n=10 per bin).



Pharmacometrics reviewer also notes "Of importance in the assessment of the exposure-response relationship, midazolam was allowed after the initiation of DEX, to rescue the patients. Since midazolam has a sedative effect, the exposure-response relationship was further evaluated to determine if midazolam was a potential confounding factor in the relationship. Figure 4 depicts a plot of individual RSSavg observations as a function of DEX steady state concentration. For each summary bin, the percentage of patients who received midazolam rescue is presented along with the median dose of midazolam used. The analysis shows that the bin with the highest RSSavg response also had the highest percentage of patients requiring midazolam rescue and, more apparent, a higher rescue dose of midazolam. This finding confounds the exposure-response relationship observed between DEX concentrations and the sedation scales."

Please refer to detailed concentration response analysis of RSSavg to Css (Figure 3 and Figure 4 of attached Pharmacometrics review).

Safety:

With regard to cardiovascular effects, interestingly hypotension and bradycardia was not recorded many patients. Only one patient in the 2 – 6 yr age group was noted to have bradycardia.

Table: Summary of Pharmacokinetic Parameters in 2 – 17 yr old patients (DEX-08-01)

Parameter/ Statistics	Dose Level 1 DEX	Dose Level 2 DEX	Dose Level 3 DEX	Dose Level 4 DEX
Primary Pharmacokinetic Parameters				
AUC_{0-t} [(pg/mL) hr] (N)	14	13	14	14
Mean (SD)	2681.332 (2353.3418)	6460.576 (3766.4657)	16992.540 (29927.3911)	28531.864 (17496.3985)
Median (Min, Max)	1540.417 (779.88, 9266.09)	5247.638 (1900.23, 12194.00)	5606.310 (4257.50, 116910.2)	25411.857 (10027.42, 68850.45)
%CV	87.77	58.30	176.12	61.32
$AUC_{0-\infty}$ [(pg/mL) hr] (N)	12	13	14	14
Mean (SD)	3153.518 (3343.3451)	6673.163 (3781.2183)	17300.539 (29935.7647)	28970.541 (17936.8970)
Median (Min, Max)	1583.539 (923.23, 12681.98)	5521.515 (2023.22, 12413.04)	6078.304 (4568.71, 117264.1)	25675.767 (10093.96, 70764.26)
%CV	106.02	56.66	173.03	61.91
C_{max} (pg/mL) (N)	14	13	14	14
Mean (SD)	480.437 (625.9946)	847.691 (633.7352)	3385.569 (7384.0699)	3090.939 (1625.5241)
Median (Min, Max)	266.465 (169.58, 2558.19)	581.040 (399.60, 2456.03)	966.235 (534.11, 28804.30)	2686.210 (1540.85, 6810.13)
%CV	130.30	74.76	218.10	52.59
T_{max} (hours) (N)	14	13	14	14
Mean (SD)	7.307 (5.7937)	8.805 (9.5105)	2.174 (2.7535)	6.815 (5.9039)
Median (Min, Max)	6.042 (0.08, 16.17)	5.683 (0.12, 20.93)	0.167 (0.08, 6.33)	5.417 (0.13, 17.60)
%CV	79.29	108.01	126.66	86.63
$t_{1/2}$ (hours) (N)	12	13	14	14
Mean (SD)	1.546 (0.3401)	1.743 (0.3018)	2.045 (0.6582)	2.145 (0.6763)
Median (Min, Max)	1.556 (1.03, 2.28)	1.687 (1.27, 2.45)	1.795 (1.24, 3.33)	2.125 (0.98, 3.33)
%CV	22.00	17.31	32.18	31.53
λz (1/hour) (N)	12	13	14	14
Mean (SD)	0.469 (0.1062)	0.408 (0.0672)	0.369 (0.1037)	0.360 (0.1350)
Median (Min, Max)	0.446 (0.30, 0.67)	0.411 (0.28, 0.54)	0.386 (0.21, 0.56)	0.326 (0.21, 0.71)
%CV	22.64	16.46	28.13	37.56
C_{ss} (pg/mL) (N)	12	13	14	14
Mean (SD)	402.026 (535.1718)	539.848 (166.7423)	1347.284 (1308.0988)	2827.144 (1169.4226)
Median (Min, Max)	197.991 (149.71, 2056.54)	513.902 (282.31, 868.84)	947.907 (637.50, 5743.55)	2665.409 (1602.66, 5429.48)
%CV	133.12	30.89	97.09	41.36
V_d (L) (N)	12	13	14	14
Mean (SD)	61.982 (66.0605)	50.632 (26.2671)	52.328 (25.5848)	62.186 (34.7628)
Median (Min, Max)	42.960 (13.76, 238.30)	40.657 (23.67, 95.26)	51.303 (17.22, 100.71)	57.802 (23.17, 138.40)
%CV	106.58	51.88	48.89	55.90

Abbreviations: CD=continuous dose; DEX=dexmedetomidine; LD=loading dose

Note: Percentages are based on the number of subjects in each treatment group.

Note: Dose Level 1- Dex LD=0.25/CD=0.2 mcg/kg/hr; Dose Level 2- Dex LD=0.50/CD=0.4 mcg/kg/hr; Dose Level 3- Dex LD=1.00/CD=0.7 mcg/kg/hr; Dose Level 4- Dex LD=1.00/CD=2.00 mcg/kg/hr

[a] By age group I, II. Group I – Ages ≥ 2 through 6 years old, Group II Ages ≥ 6 through 17 years old.

[b] Age at time of screening in years derived as (Date of Consent – Date of Birth)/365.25 and rounded to 2 decimal places.

3. Summary of Children's Hospital of Philadelphia (CHOP) Study in 1 month – 2yr old patients):

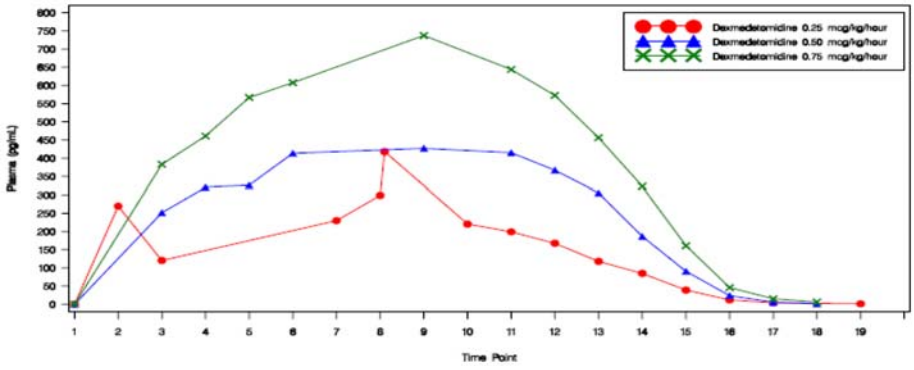
The CHOP Study was a physician sponsored Phase I, single center, dose escalation PK and PD study of a single loading dose of DEX followed by a continuous infusion for up to 24 hours in infants aged 1 month to 2 years of age. The pharmacokinetic profile demonstrated linearity and dose proportionality among 0.25, 0.50 and 0.75 mcg/kg/hour dose levels (with appropriate loading dose); as dose increased, AUC and C_{max} increased in proportion.

Table: Dose Proportionality Analysis of Dexmedetomidine Pharmacokinetic Parameters - PK Population.

	Geometric Means			
Parameter (units)	Dexmedetomidine Low Dose[a] N=12	Dexmedetomidine Moderate Dose[b] N=12	Dexmedetomidine High Dose[c] N=12	Slope[d] (95% CIs)
ıll PK Population				
n	12	12	12	
AUC_{0-t} [hr*(pg/mL)]	1804.57	4163.01	7453.03	1.282 (0.835, 1.729)
AUC_{0-inf} [hr*(pg/mL)]	1851.13	4195.77	7492.29	1.263 (0.820, 1.706)
C_{max} (pg/mL)	277.59	460.66	760.76	0.898 (0.652, 1.143)
ıge 1 to < 6 months				
n	5	4	3	
AUC_{0-t} [hr*(pg/mL)]	1630.18	4171.58	7477.55	1.380 (0.631, 2.129)
AUC_{0-inf} [hr*(pg/mL)]	1668.59	4209.96	7511.57	1.362 (0.621, 2.103)
C_{max} (pg/mL)	260.44	444.34	847.52	1.010 (0.455, 1.566)
ıge 6 to < 12 months				
n	4	6	7	
AUC_{0-t} [hr*(pg/mL)]	1542.76	4647.87	8392.11	1.541 (0.828, 2.255)
AUC_{0-inf} [hr*(pg/mL)]	1601.44	4675.95	8435.14	1.512 (0.804, 2.221)
C_{max} (pg/mL)	286.81	500.04	762.71	0.891 (0.489, 1.292)
ıge 12 to 24 months				
n	3	2	2	
AUC_{0-t} [hr*(pg/mL)]	2634.53	2979.07	4895.66	0.501 (-1.098, 2.100)
AUC_{0-inf} [hr*(pg/mL)]	2669.84	3010.96	4929.13	0.495 (-1.092, 2.083)
C_{max} (pg/mL)	295.55	387.09	641.22	0.654 (0.130, 1.177)

Source: Table 14.2.1.1.2.
a. Low dose dexmedetomidine: 0.35 mcg/kg bolus, 0.25 mcg/kg/hour infusion.
b. Moderate dose dexmedetomidine: 0.7 mcg/kg bolus, 0.5 mcg/kg/hour infusion.
c. High dose dexmedetomidine: 1.0 mcg/kg bolus, 0.75 mcg/kg/hour infusion.
d. Estimate slopes were computed from linear regression of log (PK parameters) versus log (dose) over dose range.
CI=confidence interval.

Figure: Mean Plasma Dexmedetomidine over Time in neonates.



Pharmacodynamics (CHOP Study in 1 month – 2yr old patients):

A summary of the level of sedation, measured with the UMSS, at each time point during the treatment period for the enrolled population is presented. Patients had deep sedation (UMSS 3-4) from pre-dose to 2 hours after infusion, and maintained a moderate level of sedation (UMSS 1-3) after 4 hours infusion through the end of infusion for all dose levels. The summary of pediatric patients sedated for varying durations is listed in the table below.

	Number (%) of Patients			
Time Point Characteristic	**Low Dose[a] N=12**	**Moderate Dose[b] N=12**	**High Dose[c] N=12**	**p-values[d]**
Pre-bolus/Baseline				0.5788
Awake and alert	0	0	0	
Minimally sedated/ Sleepy	1(8.3)	0	0	
Moderately sedated/ Somnolent	0	0	0	
Deeply sedated/ Deep sleep	0	1 (8.3)	1 (8.3)	
Unarousable	11 (91.7)	11 (91.7)	10 (83.3)	
Post-bolus/Pre-infusion				0.4288
Awake and alert	0	0	0	
Minimally sedated/ Sleepy	1 (8.3)	0	0	
Moderately sedated/ Somnolent	0	1 (8.3)	0	
Deeply sedated/ Deep sleep	1 (8.3)	2 (16.7)	0	
Unarousable	10 (83.3)	9 (75.0)	11 (91.7)	
Post Infusion Hour 1				0.4880
Awake and alert	0	0	0	
Minimally sedated/ Sleepy	1 (8.3)	0	0	
Moderately sedated/ Somnolent	1 (8.3)	0	2 (16.7)	
Deeply sedated/ Deep sleep	1 (8.3)	3 (25.0)	1 (8.3)	
Unarousable	9 (75.0)	9 (75.0)	8 (66.7)	
Post Infusion Hour 3				0.1834
Awake and alert	0	0	0	
Minimally sedated/ Sleepy	2 (16.7)	2 (16.7)	1 (8.3)	
Moderately sedated/ Somnolent	3 (25.0)	2 (16.7)	4 (33.3)	
Deeply sedated/ Deep sleep	7 (58.3)	3 (25.0)	2 (16.7)	
Unarousable	0	5 (41.7)	4 (33.3)	
Post Infusion Hour 6				0.8306
Awake and alert	0	1 (8.3)	1 (8.3)	
Minimally sedated/ Sleepy	2 (16.7)	3 (25.0)	0	
Moderately sedated/ Somnolent	7 (58.3)	5 (41.7)	6 (50.0)	
Deeply sedated/ Deep sleep	1 (8.3)	2 (16.7)	2 (16.7)	
Unarousable	1 (8.3)	1 (8.3)	1 (8.3)	

Post Infusion Hour 10				0.5512
Awake and alert	3 (25.0)	1 (8.3)	3 (25.0)	
Minimally sedated/ Sleepy	2 (16.7)	4 (33.3)	2 (16.7)	
Moderately sedated/ Somnolent	1 (8.3)	4 (33.3)	1 (8.3)	
Deeply sedated/ Deep sleep	2 (16.7)	1 (8.3)	3 (25.0)	
Unarousable	0	1 (8.3)	0	
Post Infusion Hour 14				0.5683
Awake and alert	2 (16.7)	2 (16.7)	4 (33.3)	
Minimally sedated/ Sleepy	0	3 (25.0)	2 (16.7)	
Moderately sedated/ Somnolent	4 (33.3)	3 (25.0)	2 (16.7)	
Deeply sedated/ Deep sleep	2 (16.7)	1 (8.3)	1 (8.3)	
Unarousable	0	0	0	
Post Infusion Hour 18				0.3840
Awake and alert	0	1 (8.3)	2 (16.7)	
Minimally sedated/ Sleepy	2 (16.7)	3 (25.0)	0	
Moderately sedated/ Somnolent	2 (16.7)	1 (8.3)	2 (16.7)	
Deeply sedated/ Deep sleep	1 (8.3)	0	0	
Unarousable	0	1 (8.3)	0	
Post Infusion Hour 22				0.4821
Awake and alert	1 (8.3)	1 (8.3)	0	
Minimally sedated/ Sleepy	0	0	0	
Moderately sedated/ Somnolent	2 (16.7)	0	1 (8.3)	
Deeply sedated/ Deep sleep	0	0	0	
Unarousable	0	1 (8.3)	0	
Post Infusion Hour 26				--
Awake and alert	0	0	0	
Minimally sedated/ Sleepy	1 (8.3)	0	0	
Moderately sedated/ Somnolent	0	0	0	
Deeply sedated/ Deep sleep	0	0	0	
Unarousable	0	0	0	

Source: Table 14.2.2.2
a. Low-dose dexmedetomidine (0.35 mcg/kg bolus, 0.25 mcg/kg/hour infusion).
b. Moderate-dose dexmedetomidine (0.7 mcg/kg bolus, 0.5 mcg/kg/hour infusion).
c. High-dose dexmedetomidine (1.0 mcg/kg bolus, 0.75 mcg/kg/hour infusion).
d. P-values are from Cochran-Mantel-Haenszel test.
Note: Patient 33 UMSS scores were not applicable due to continuous infusion of neuromuscular blockade.

ITT=Intent-to-Treat, --=not applicable, N=number of patients, UMSS=University of Michigan Sedation Scale

4. Summary of Study DEX-11-01 was a Phase II, open-label, single center, pharmacokinetic and pharmacodynamic study of DEX in pediatric subjects aged 12 months through < 24 months old, with DEX administered as an IV loading dose followed by a continuous IV infusion. This study was conducted to complete population requirements not met by CHOP. A total of 5 subjects were randomized at 1 site in the United States. Two subjects were randomized to dose level 1 and 3 subjects to dose level 2. PK results of these subjects are discussed in the context of population PK analysis (See attached Pharmacometrics review).

5. Summary of Study-09-08 (PK and PD experience in term and pre-term neonates):

Study DEX-09-08 was a Phase II/III, open-label, multicenter, safety, efficacy and pharmacokinetic study of DEX administered as an IV loading dose followed by a continuous IV infusion in neonates ≥ 28 weeks to ≤ 44 weeks gestational age who were initially intubated and mechanically ventilated.

Subjects were preterm neonates ≥ 28 weeks through < 36 weeks gestational age and term neonates born at ≥ 36 weeks through ≤ 44 weeks gestational age, in an intensive care setting anticipated to require a minimum of 6 hours of continuous IV sedation. The primary efficacy end point was the percentage of subjects who received rescue midazolam for sedation during the DEX infusion while intubated. The dosing scheme for the study and results of the primary efficacy analysis are presented in the table below.

Table. Efficacy results for Study DEX-09-08

Group	Dose Level 1 (N = 14)	Dose Level 2 (N = 14)	Dose Level 3 (N = 8)	Total (N = 36)
Number of Subjects Who Received Rescue Midazolam				
Age Group I	0/6 (0%)	0/6 (0%)	--	0/12 (0%)
Age Group II	1/8 (12.5%)	1/8 (12.5%)	2/8 (25%)	4/24 (16.7%)
Combined Groups	1/14 (7.1%)	1/14 (7.1%)	2/8 (25%)	4/36 (11.1%)
Number of Subjects Who Did Not Receive Rescue Midazolam				
Age Group I	6/6 (100%)	6/6 (100%)	-	12/12 (100%)
Age Group II	7/8 (87.5%)	7/8 (87.5%)	6/8 (75%)	20/24 (83.3%)
Combined Groups	13/14 (92.9%)	13/14 (92.9%)	6/8 (75%)	32/36 (88.9%)

Data presented as number and % of Efficacy Evaluable subjects who received or did not receive midazolam for sedation during the DEX infusion within each dose level by Age Group.
Age Group I = ≥ 28 to < 36 weeks gestational age; Age Group II = ≥ 36 to ≤ 44 weeks gestational age.
N = number of Efficacy Evaluable subjects at given Dose Level.
Dose Level 1 is 0.05 mcg/kg loading dose, 0.05 mcg/kg/hour maintenance dose.
Dose Level 2 is 0.1 mcg/kg loading dose, 0.1 mcg/kg/hour maintenance dose.
Dose Level 3 is 0.2 mcg/kg loading dose, 0.2 mcg/kg/hour maintenance dose.
Source: DEX-09-08 Interim Study Report, Table 14.2.1.1; DEX-09-08 Addendum to the Interim Study Report, Table 14.2.1; Data on File WW SEP2012.

Pharmacokinetic data from the study DEX-09-08 was utilized in the population PK analysis.

2 General Attributes

2.1 Regulatory Background

Hospira Inc. submitted a pediatric efficacy supplement to the New Drug Application (NDA 21-038) on 12/17/2012.

Previously, Precedex was approved for adult use in intensive care unit sedation of initially intubated mechanically ventilated patients (12/17/1999); it is also approved for adult use in sedation of non-intubated patients prior to and/or during surgical and other procedures. (10/17/2008).

The pediatric clinical studies and trials were executed to fulfill the requirements of the Agency issued Pediatric Written Request (Final Amendment dated 8/30/2011).

The formulation of dexmedetomidine (Precedex) that has been used in the pediatric studies described in this supplemental New Drug Application (sNDA) is the current FDA-approved formulation of Precedex commercially marketed for intravenous infusion following dilution.

2.2 General Clinical Pharmacology

Brief Description of clinical pharmacology of dexmedetomidine in adults is as follows:

Dexmedetomidine is intended for sedation and analgesia in an intensive care setting Unit (ICU) and is claimed to produce titratable, predictable sedation, from which patients are easily arousable and cooperative. Chiral inversion of dexmedetomidine to the inactive *levo* isomer is likely to be insignificant. Recovery of the radiolabel in the mass balance study was complete and quantitative. The excretion of the radioactivity was rapid with about 85% recovered in the urine within 24 hours post dosing. Dexmedetomidine undergoes complete biotransformation *in vivo* with very little excreted unchanged in the urine or feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. Direct N-glucuronidation to the inactive G-DEX-1 and G-DEX-2 conjugates accounts for about 34% of its metabolism.

Aliphatic hydroxylation of dexmedetomidine (mediated primarily by CYP2A6) to generate 3-hydroxy dexmedetomidine, glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine represents about 14% of the metabolism. N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl-O-glucuronide dexmedetomidine accounted for about 18% of the metabolism.

Approximately, 28% of the urinary metabolites have not been identified. The average plasma protein binding of dexmedetomidine was 94%. The specific plasma protein to which dexmedetomidine binds is unknown.

Dexmedetomidine exhibits dose-independent pharmacokinetics in the dosage regimen (b) (4) The product label describes a range of 0.3 to 1.25 ng/mL

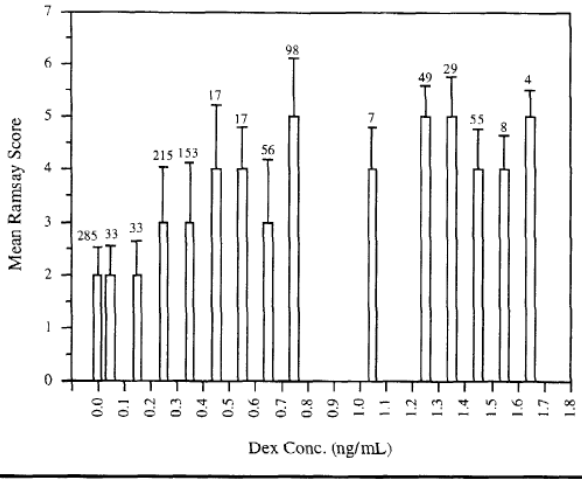
of target plasma concentrations that can be achieved by employing various rates of loading and maintenance infusions.

The main pharmacokinetic parameter values were consistent across several studies with varied infusion regimens (10 minute infusion, two-stage regimens (loading dose + maintenance dose), three-stage regimens (two loading doses + maintenance dose), and virtually continuously changing infusion rate regimens) and are as follows; The clearance is about 39.0 liter/hr, the terminal half-life is about 2 hours, and the steady state volume of distribution is about 1.3 liter/kg.

Dexmedetomidine did not show gender and age differences in pharmacokinetics of adult subjects. Therefore, based on pharmacokinetic considerations no dosage adjustments are warranted in females or in the elderly.

Dexmedetomidine pharmacokinetics were not affected in patients with severe renal impairment after a single dose administration of dexmedetomidine.

Figure: Plasma concentration to Mean Ramsay sedation score noted in Phase 2 study in adults.



[a] For each Ramsay score, a dexmedetomidine plasma concentration (ng/mL) was linearly interpolated from the surrounding dexmedetomidine values, if not measured. A mean Ramsay score was then calculated for each 0.1 ng/mL increment of dexmedetomidine. Each bar is centered over the mean of the dexmedetomidine increment and represents the mean Ramsay score for that dexmedetomidine concentration range. The number above each bar is the number (N) of Ramsay scores used to compute the mean at that dexmedetomidine concentration range. Bars comprising of less than 4 values were omitted.

Data from previously reviewed (original NDA 21-038) adult study Dex-97-028, a dose ranging study, indicates concentrations above 0.3 ng/mL may be effective in producing RSS of >3 (acceptable level of sedation).

The main pharmacokinetic parameter values were consistent across several studies with varied infusion regimens (10 minute infusion, two-stage regimens (loading dose + maintenance dose), three-stage regimens (two loading doses + maintenance dose), and virtually continuously changing infusion rate regimens) and are as follows; The clearance is about 39.0 liter/hr, the terminal half-life is about 2 hours, and the steady state volume of distribution is about 1.3 liter/kg.

Dexmedetomidine did not show gender and age differences in pharmacokinetics of adult subjects. Therefore, based on pharmacokinetic considerations no dosage adjustments are warranted in females or in the elderly.

Dexmedetomidine pharmacokinetics were not affected in patients with severe renal impairment after a single dose administration of dexmedetomidine.

2.3 Analytical

Because of the age range (≥ 28 weeks gestational age to < 17 years of age) of subjects covered by these studies, particularly for the extremely young neonates, bioanalytical methods were developed to determine the plasma concentrations of DEX in small volume samples obtained from the subjects. The bioanalytical methods used were similar across studies DEX-08-01, DEX-11-01, DEX-09-08, and the CHOP study. In general, dexmedetomidine was extracted from a ≤ 0.050 mL aliquot of human lithium heparinized plasma using an automated protein precipitation procedure. The extracted samples were then analyzed utilizing a validated high performance liquid chromatographic method with tandem mass spectrometry detection (HPLC-MS/MS) and automated extraction. The validation of these methods is detailed under each of the individual studies.

Summary of main validation results for bioanalytical methods for DEX-08-01

Parameter	Result
Linearity	$r^2 \geq 0.9977$
Calibration Curve Range	30.54 to 3054.00 pg/mL
Between-Run Accuracy	QC % nominal concentrations: 98.33 to 101.20%
Between-Run Precision	QC coefficients of variation: 2.93 to 3.44%
Within-Run Accuracy	QC % nominal concentrations: 94.46 to 104.88%
Within-Run Precision	QC coefficients of variation: 1.15 to 3.68%
Recovery of Analyte	QC means: 106.71, 100.97 and 100.43%
Recovery of Internal Standard	Mean: 102.76%
Lower Limit of Quantitation (LLOQ)	30.54 pg/mL with a signal to noise ratio of 35
Dilution Integrity Accuracy	QC % nominal concentrations: 100.24 and 104.20%
Dilution Integrity Precision	QC coefficients of variation: 2.25 and 1.61%
Source: Bioanalytical Report for Study DEX-08-01, dated 28 October 2010.	

Summary of main validation results for bioanalytical methods for Studies DEX-11-01 and DEX-09-08.

Parameter	Result
Linearity	$r^2 \geq 0.9977$
Calibration Curve Range	30.54 to 3054.00 pg/mL
Between-Run Accuracy	QC % nominal concentrations: 98.33 to 101.20%
Between-Run Precision	QC coefficients of variation: 2.93 to 3.44%
Within-Run Accuracy	QC % nominal concentrations: 94.46 to 104.88%
Within-Run Precision	QC coefficients of variation: 1.15 to 3.68%
Recovery of Analyte	QC means: 106.71, 100.97 and 100.43%
Recovery of Internal Standard	Mean: 102.76%
Lower Limit of Quantitation (LLOQ)	30.54 pg/mL with a signal to noise ratio of 35
Dilution Integrity Accuracy	QC % nominal concentrations: 100.24 and 104.20%
Dilution Integrity Precision	QC coefficients of variation: 2.25 and 1.61%
Source: Bioanalytical Report for Study DEX-11-01, dated 17 August 2011.	

Summary of main validation results for bioanalytical methods used in CHOP Study

Parameter	Result
Linearity	$r \geq 0.998$
Calibration Curve Range	5 to 1500 pg/mL
Intra-day Accuracy	QC % nominal concentrations: 90.2 to 101%
Intra-day Precision	QC coefficients of variation:1.04 to 6.84%
Inter-day Accuracy	QC % nominal concentrations: 92.7 to 98.6%
Inter-day Precision	QC coefficients of variation: 4.08 to 5.37%
Recovery of Analyte	QC means: 78.32, 77.59 and 76.59%
Recovery of Internal Standard	95.5 to 103%
Lower Limit of Quantitation (LLOQ)	5 pg/mL with a signal to noise ratio of 10
Source Reference 2.	

Comparison and Analyses of Results Across Studies

In the four most recently completed PK studies, bioanalytic methods utilizing extraction of dexmedetomidine from human lithium heparinized plasma and analysis by liquid chromatography and tandem mass spectrometry detection were employed. In three of the studies (DEX-08-01, DEX-09-08, and DEX-11-01), the bioanalytic analyses and validations were conducted by (b) (4), and in the fourth study, the bioanalytic analyses and validations were conducted by (b) (4) In all four studies, the methods demonstrated linearity across a two order-of-magnitude range, with accuracy and precision between and within runs (in the case of (b) (4)) and for intra-day and inter-day runs (in the case of (b) (4), and with accuracy and precision for dilution integrity (in the case of (b) (4)). The (b) (4) analyses showed greater percent recovery of analyte than (b) (4) (> 100% vs. approximately 77%), while (b) (4) showed a more sensitive lower limit of quantitation than (b) (4) (5 pg/mL vs. approximately 30 pg/mL).

3 Labeling

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

----------*DOSAGE AND ADMINISTRATION*----------

(b) (4)

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(b) (4)

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4.2 Pharmacometrics Review by Dr. Satjit Brar.

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRICS REVIEW

NDA Number	21038
Brand Name	Precedex
Drug Components	Dexmedetomidine HCl
(b) (4)	(b) (4)
Pharmacometrics Reviewer	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Sponsor	Hospira

1 Summary of Findings

1.1 Key Review Questions

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

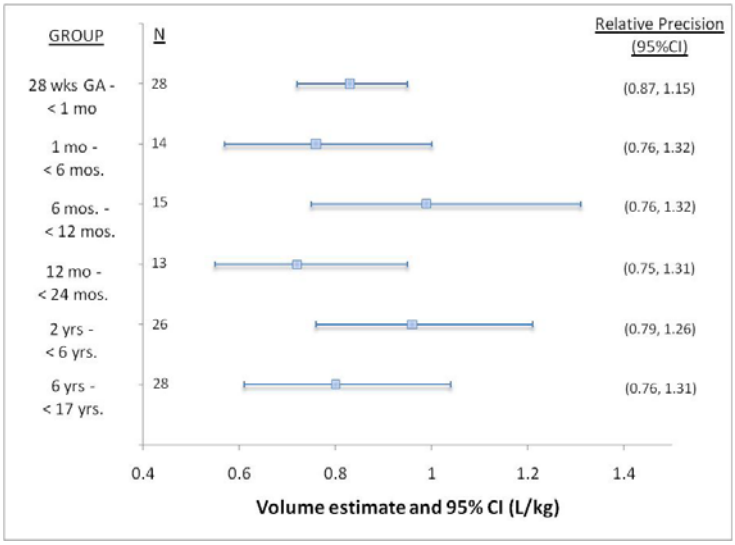
1.1.1 Has the pharmacokinetics of dexmedetomidine (DEX) been adequately characterized in the pediatric population?

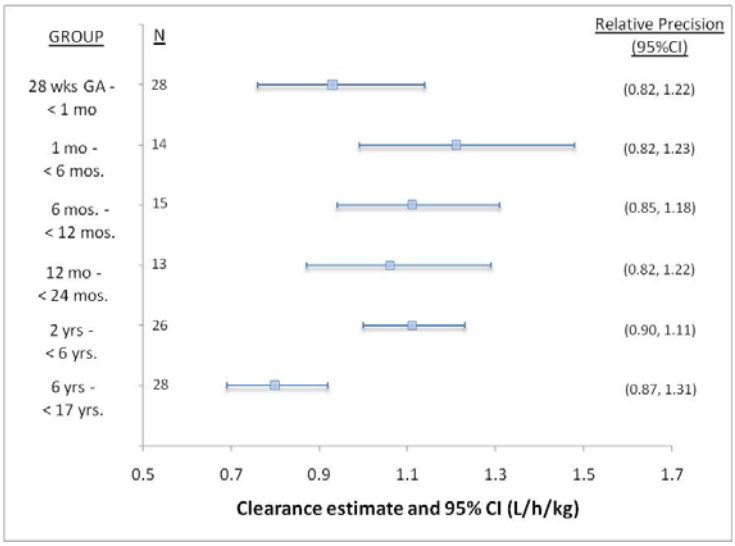
The PK of DEX has been characterized, with adequate precision, for different pediatric age groups from 28 weeks gestational age to <17 years. A population PK model was generated from PK information that included rich sampling data available from four PK studies performed in a patient population of n=131 subjects. Various loading and maintenance doses were employed to assess the PK of DEX in the pediatric population.

Clearance and volume of distribution increased with increasing age and values of weight-adjusted clearance decreased with increasing age, approaching values expected in adults. Weight-adjusted volume of distribution was constant across the age groups. There was a lower weight-adjusted clearance observed in neonates compared to infants which may be attributed to a lack of maturation of clearance mechanisms in neonates. A forest plot depicting the geometric

means and 95%CI of the weight-adjusted volume of distribution and clearance, by age group, is presented in Figure 1 below. Upon evaluation of the relative precision for clearance and volume of distribution estimates, all 95% CI are within the bounds of 0.60 – 1.40, the threshold used to design pediatric PK studies to ensure adequate precision of PK parameters. Based on this comparison, the reviewer concludes that the PK information obtained for each age group has been adequately characterized.

Figure 1. Forest Plot of the Geometric mean and 95%CI of Weight-adjusted Volume (top) and Clearance (bottom) along with the Relative Precision (right-column, 95%CI). Age group categories and number of subjects per group are presented on the left columns.

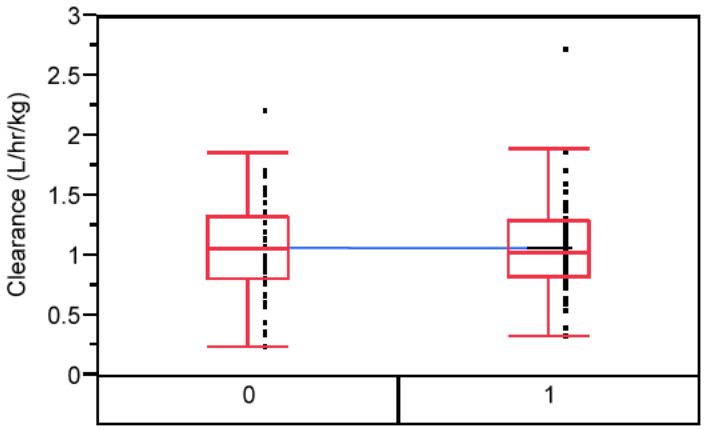




1.1.2 What is the influence of Cardiopulmonary Bypass (CPB) on DEX Clearance?

According to the current analysis, the CPB procedure itself did not have an influence on DEX clearance. Covariate effects were tested on DEX clearance and volume based on physiologic plausibility, but no effect met the pre-specified criteria for inclusion in the model. The plot in Figure 2 below depicts the weight-adjusted clearance as a function of CPB.

Figure 2. Weight-adjusted clearance as a function of Cardio-Pulmonary Bypass (CPB, 0 = No and 1 = Yes). Observed points represent individual body weight adjusted clearance. The box-plot represents the distribution of the observations and the blue solid line connects the means between the groups. For the groups, n=43 subjects did not have CPB while n=81 subjects had CPB.



Patients who underwent CPB had an average body-weight adjusted clearance of 1.07 (95% CI 1.04 – 1.11) L/hr/kg, while and patients who did not have the procedure had an average body-weight adjusted clearance of 1.1 (95% CI 1.05 – 1.13) L/hr/kg (p-value >0.05).

This result is in contrast to a previously developed 2-compartment population PK model of dexmedetomidine in infants (aged 1 to 24 months) after open heart surgery.* In this published model, significant covariate effects included total bypass time on clearance. The data available for covariate assessment differed from Su et al., where total bypass time was determined to be a significant covariate as a continuous variable. The current analysis was limited to evaluation of CPB use as a dichotomous variable indicating occurrence or lack of occurrence.

**Su F, Nicolson SC, Gastonguay MR, et al. Population pharmacokinetics of dexmedetomidine in infants after open heart surgery. Anesth Analg. 2010; 110:1383-1392.*

1.1.3 Does the exposure-response relationship [redacted] (b) (4)

Although exposure-response relationships for DEX showed a trend with respect to sedation scales, the analysis was confounded by the concomitant use of midazolam in Study DEX-08-01. Patients that achieved the highest DEX concentrations, and largest effects on sedation, also had larger doses of midazolam compared to those patients with lower DEX concentrations and lower sedative effect. For this reason, the analysis was inconclusive in determining whether the dosing regimen is supported by the exposure-response relationship.

The [redacted] (b) (4) have been studied in the pivotal and supportive pediatric clinical studies (see Table 2). It is important to note that none of the endpoints (primary or secondary) met statistical significance for the pivotal, randomized trial (Study DEX-08-05).

In order to assess the concentration-response relationship of DEX on sedation, PK/PD information from Study DEX-08-01 was analyzed. Study DEX-08-01 was a Phase II, open-label, dose ranging study which enrolled n=59 subjects aged 2 to < 17 years. DEX was administered as an intravenous (IV) loading dose followed by IV maintenance infusion (from 6 hrs up to 24 hours). The dose levels used in this trial are shown in the **Table 1**. Midazolam and fentanyl were allowed, after the initiation of DEX, to rescue the patients and manage pain, respectively.

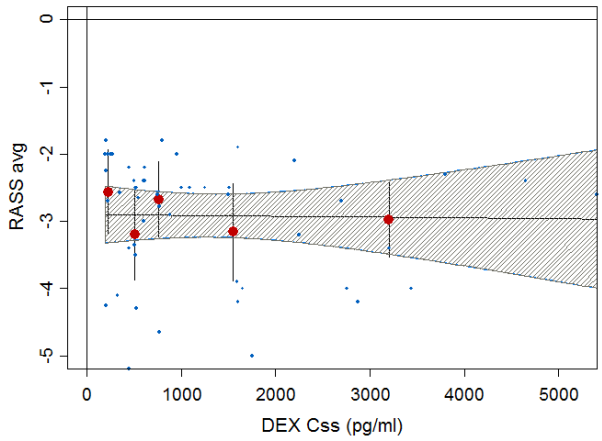
Table 1. Dexmedetomidine Doses used in Study DEX-08-01

Age Group I (Ages ≥ 2 through <6 years old) Age Group II (Ages ≥ 6 through <17 years old)	Loading Dose (10 minutes)	Maintenance Dose (at least 6 hours and up to 24 hours)	Post-Treatment Period
Dose Level 1	0.25 mcg/kg	0.2 mcg/kg/hr	24 hours
Dose Level 2	0.50 mcg/kg	0.4 mcg/kg/hr	24 hours
Dose Level 3	1.00 mcg/kg	0.7 mcg/kg/hr	24 hours
Dose Level 4	1.00 mcg/kg	2.0 mcg/kg/hr	24 hours

Two sedation endpoints were evaluated to assess their relationship with DEX concentrations, the Ramsay Sedation Scale (RSS, scaled from 1 to 6 where higher the number, more the sedation) and the Richmond Agitation Sedation Scale (RASS, scaled from +4 to -5 where lower the number, more the sedation). Since all subjects had PK and PD data up to 6 hours of maintenance dosing, the exposure-response analysis used this timeframe for the assessment (from initiation of the loading dose to 6 hours of maintenance dosing). Individual average sedation scale measures (from 0-6 hours) was analyzed as a function of steady state DEX concentration (Css, pg/ml) for RSS and RASS. Representative examples of individual time-course data of RSS, overlayed with DEX concentration for the first 6 hours are presented in Figur. Since steady state concentrations were achieved within 2 hours, the exposure-response assessment evaluated Css as an exposure metric for comparison to the sedation scores. As RSS and RASS fluctuated over the time course of dosing, an average sedation score was computed for each individual and compared to DEX Css for the exposure-response analysis.

For $RASS_{avg}$, an exposure-response relationship was not observed using a linear model (Figure 3). Regardless of steady state DEX concentration, an increase in effect (decrease of RASS scale) was not observed.

Figure 3. Individual Average Richmond Agitation Sedation Scale, RASS (from 0-6 hours), as a function of steady state DEX concentration from Study DEX-08-01. A total of n=50 pediatric subjects informed the analysis (n=10 per bin). A non-significant slope was observed for the linear model.



Note: For exposure-response relationships, Blue dots represent individual observations while solid red symbols and bars represent the mean and 95% confidence interval of RASS for each DEX Css quantile. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval (shaded region).

On the other hand, the analysis of RSS_{avg} yielded a positive relationship with DEX concentration (p-value <0.05 for slope of the linear relationship). With an increase in DEX steady state concentrations, increased sedation (i.e., increase in RSS_{avg}) was observed (Figure 4). It is important to note that the observed relationship is driven by the observations within the far-right quantile (at concentrations >2500 pg/ml). Below these concentrations, the quantile binned data suggests no relationship.

Of importance in the assessment of the exposure-response relationship, midazolam was allowed after the initiation of DEX, to rescue the patients. Since midazolam has a sedative effect, the exposure-response relationship was further evaluated to determine if midazolam was a potential confounding factor in the relationship. Figure 4 depicts a plot of individual RSS_{avg} observations as a function of DEX steady state concentration. For each summary bin, the percentage of patients who received midazolam rescue is presented along with the median dose of midazolam used. The analysis shows that the bin with the highest RSS_{avg} response also had the highest percentage of patients requiring midazolam rescue and, more apparent, a higher rescue dose of midazolam. This finding confounds the exposure-response relationship observed between DEX concentrations and the sedation scales.

Figure 4. Individual Average Ramsay Sedation Scale, RSS (from 0-6 hours), as a function of steady state DEX concentration from Study DEX-08-01. A total of n=50 pediatric subjects informed the analysis (n=10 per bin).

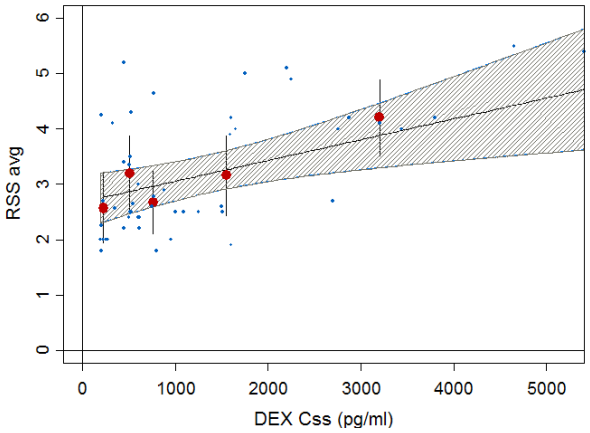
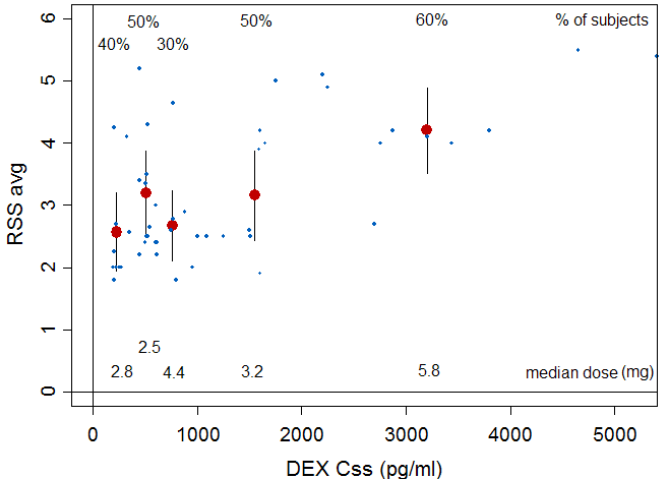


Figure 5. Midazolam (MDZ) Analysis of Individual Average Ramsay Sedation Scale, RSS (from 0-6 hours), as a function of steady state DEX concentration. A total of n=50 pediatric subjects informed the analysis (n=10 per bin) from Study DEX-08-01. Numbers above bins represent the percentage of subjects within the bin that were given rescue midazolam. The median dose of midazolam given (mg) per bin is represented below the bin. Table of numeric values presented below plot.



Bin	1	2	3	4	5
mean Rss_{avg}	2.57	3.20	2.67	3.16	4.21
median DEX Css (pg/mL)	222	507	760	1550	3201
%subjects MDZ rescue	40%	50%	30%	50%	60%
median dose of MDZ (mg)	2.8	2.5	4.4	3.2	5.8

1.2 Recommendations

The Pharmacometrics reviewer finds the quality of pediatric pharmacokinetic data acceptable. However, no dosing recommendation can be given based on the efficacy and safety results of the pediatric trials performed.

1.3 Label Statements

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

2 ----------DOSAGE AND ADMINISTRATION----------

(b) (4)

12.3 Pharmacokinetics

(b) (4)

[redacted] (b) (4)

3 Pertinent regulatory background

Dexmedetomidine HCl Injection (DEX) (Precedex®), a lipophilic alpha-2 agonist derivative is an intravenous sedative indicated for sedation. DEX was approved by the Food and Drug Administration (FDA) on 17 December 1999 for the sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting for up to 24 hours at an initial dose of 1 mcg/kg over 10 minutes followed by a maintenance dose titrated between 0.2 and 0.7 mcg/kg/hr. DEX was also approved by the FDA in October 2008 (NDA #21-038/S-010) for adults during non-intubated sedation prior to and/or during surgical and other procedures at maintenance dosages of 0.2 to 1.0 mcg/kg/hr following a loading dose of 1.0 mcg/kg over 10 minutes.

The current sNDA is being submitted in response to a Pediatric Written Request (PWR) [redacted] (b) (4) In accordance with the requirements of the PWR, this application outlines the pharmacokinetic, efficacy, and safety data in the six PWR-specified Age Groups, [redacted] (b) (4)

4 Results of Sponsor's Analysis

Hospira completed a total of seven clinical studies in pediatric subjects in support of the PWR for DEX for the [redacted] (b) (4) DEX-08-05, DEX-09-08 and DEX-11-06 are pivotal studies, and Children's Hospital of Philadelphia (CHOP), DEX-08-01 and DEX-11-01 are supportive studies. An overview of the design of these studies is presented in **Table 2** below.

Table 2. Overview of Dexmedetomidine Studies in Pediatric Subjects

Study Number	Study Description	Dose Regimens (Loading Dose + Maintenance Dose)	Number of Subjects	Data Collected
DEX-08-05*	A Phase III, Randomized, Double-blind, Dose-controlled, Multi-center Study to Evaluate Safety and Efficacy of Dexmedetomidine (DEX) in Intubated and Mechanically Ventilated Pediatric Intensive Care Unit Subjects (1 month to < 17 years old)	Dose Level 1 0.2 mcg/kg + 0.2 mcg/kg/hr (0.025–0.5 mcg/kg/hr titration) 0.3 mcg/kg + 0.3 mcg/kg/hr (0.05 – 0.5 mcg/kg/hr titration) Dose Level 2 0.5 mcg/kg + 0.5 mcg/kg/hr (0.1 – 0.7 mcg/kg/hr titration) 0.6 mcg/kg + 0.6 mcg/kg/hr (0.2 – 1.4 mcg/kg/hr titration)	73 102	Safety Efficacy
DEX-09-08*	A Phase II/III, Open-label, Multicenter, Safety, Efficacy and Pharmacokinetic Study of Dexmedetomidine in Neonates Ages ≥ 28 Weeks to ≤ 44 Weeks Gestational Age	Dose Level 1 0.05 mcg/kg +0.05 mcg/kg/hr Dose Level 2 0.1 mcg/kg +0.1 mcg/kg/hr Dose Level 3 0.2 mcg/kg + 0.2 mcg/kg/hr	14 14 8	PK Safety Efficacy
DEX-11-06*	A Phase II/III, Open-label, Multicenter, Safety, and Efficacy Study of Dexmedetomidine in Preterm Subjects Ages ≥ 28 Weeks to < 36 Weeks Gestational Age	0.2 mcg/kg + 0.2 mcg/kg/hr	6	Safety Efficacy

Study Number	Study Description	Dose Regimens (Loading Dose + Maintenance Dose)	Number of Subjects	Data Collected
CHOP	The Pharmacokinetics, Pharmacogenetics, and Pharmacodynamics of Dexmedetomidine in Infants Post-operative from Cardiac Surgery (> 1 mo to < 2 years old)	Dose Level 1 0.35 mcg/kg + 0.25 mcg/kg/hr Dose Level 2 0.7 mcg/kg + 0.5 mcg/kg/hr Dose Level 3 1.0 mcg/kg +0.75 mcg/kg/hr	12 12 14	PK PD Safety
DEX-08-01	A Phase II, Open-label, Multicenter, Escalating Dose, Study to Determine Pharmacokinetic and Pharmacodynamic Profile of Dexmedetomidine in Pediatric Subjects Aged ≥ 2 years old through < 17 years old	Dose Level 1 0.25 mcg/kg + 0.2 mcg/kg/hr Dose Level 2 0.5 mcg/kg + 0.4 mcg/kg/hr Dose Level 3 1.0 mcg/kg + 0.7 mcg/kg/hr Dose Level 4 1.0 mcg/kg + 2.0 mcg/kg/hr	16 14 15 14	PK PD Safety
DEX-11-01	A Phase II, Randomized, Open-label, Single Center, Pharmacokinetic and Pharmacodynamic Study of Dexmedetomidine in Pediatric Subjects Aged 12 months through < 24 months	Dose Level 1 0.7 mcg/kg + 0.5 mcg/kg/hr Dose Level 2 1.0 mcg/kg +0.75 mcg/kg/hr	2 3	PK PD Safety
W98-266	A Phase I, Open-label, Escalating Dose, No-infusion control, Pharmacokinetic and Pharmacodynamic Study of Dexmedetomidine in Pediatric Subjects Aged 2 to 12 yrs	Dose Level 1 0.33 mcg/kg Loading Dose only Dose Level 2 0.67 mcg/kg Loading Dose only Dose Level 3 1.00 mcg/kg Loading Dose only	8 8 8	PK PD Safety
*Pivotal Study. Abbreviations: DEX = demedetomidine; hr = hour; kg = kilogram; mcg = microgram; PD = pharmacodynamics; PK = pharmacokinetics.				

4.1 Overall Efficacy Results

4.1.1 Pivotal studies

DEX-08-05 was a Phase III, randomized, double-blind, multi-center, dose-controlled study evaluating the safety and efficacy of DEX in initially intubated and mechanically ventilated pediatric subjects in the pediatric intensive care setting. The study population consisted of initially intubated and mechanically ventilated pediatric subjects, aged 1 month (if premature, corrected for gestational age until 3 months of actual birth age) of age through <17 years old, that required sedation in an intensive care setting for up to 24 hours. A total of 175 subjects were enrolled. Subjects were randomized into either a low-dose or high-dose DEX treatment group, with each treatment group receiving an optional loading dose over 10 to 20 minutes and a maintenance dose for up to 24 hours. The dosing scheme is presented in the table below.

Table 3. Dosing scheme for Study DEX-08-05

	Treatment Groups	
	Dose Level 1	**Dose Level 2**
S/P Cardiopulmonary Bypass	LD*: 0.2 mcg/kg MD: 0.025-0.5 mcg/kg/hr	LD*: 0.5 mcg/hr MD: 0.1-0.7 mcg/kg/hr
All other diagnoses	LD*: 0.3 mcg/kg MD: 0.05-0.5 mcg/kg/hr	LD*: 0.6 mcg/kg MD: 0.2-1.4 mcg/kg/hr

*Loading dose was optional.
Abbreviations: CSR = clinical study report; DEX = dexmedetomidine; hr = hour; kg = kilogram; LD = loading dose (administered over 10-20 minutes); mcg = microgram; MD = maintenance dose (titration range); S/P = status-post.
Source: DEX-08-05 CSR, Figure 2.

Source: 2.7.3 Summary of Clinical Efficacy, pg 13

The primary efficacy end point was the percentage of subjects that did not require rescue midazolam for sedation based on achieving and maintaining a target UMSS range of 1-3 while intubated. There was a non-significant (p = 0.2751) dose-response effect observed with more subjects (54.3%) in the combined Dose Level 2 Group not requiring rescue midazolam to maintain the target sedation than in the combined Dose Level 1 Group (44.6%), irrespective of age. There were no statistical differences between DEX dose groups in the absolute time or percentage of time subjects were in the target sedation range (UMSS 1 to 3). No other secondary endpoints met statistical significance.

DEX-09-08 was a Phase II/III, open-label, multicenter, safety, efficacy and pharmacokinetic (PK) study of DEX administered as an intravenous (IV) loading dose followed by a continuous IV infusion in neonates ≥ 28 weeks to ≤ 44 weeks gestational age who were initially intubated and mechanically ventilated. Subjects were preterm neonates ≥ 28 weeks through < 36 weeks gestational age and term neonates born at ≥ 36 weeks through ≤ 44 weeks gestational age, in an intensive care setting anticipated to require a minimum of 6 hours of continuous IV sedation. The primary efficacy end point was the percentage of subjects who received rescue midazolam for sedation during the DEX infusion while intubated. The dosing scheme for the study and results of the primary efficacy analysis are presented in the table below.

Table 4. Efficacy results for Study DEX-09-08

Group	Dose Level 1 (N = 14)	Dose Level 2 (N = 14)	Dose Level 3 (N = 8)	Total (N = 36)
Number of Subjects Who Received Rescue Midazolam				
Age Group I	0/6 (0%)	0/6 (0%)	--	0/12 (0%)
Age Group II	1/8 (12.5%)	1/8 (12.5%)	2/8 (25%)	4/24 (16.7%)
Combined Groups	1/14 (7.1%)	1/14 (7.1%)	2/8 (25%)	4/36 (11.1%)
Number of Subjects Who Did Not Receive Rescue Midazolam				
Age Group I	6/6 (100%)	6/6 (100%)	-	12/12 (100%)
Age Group II	7/8 (87.5%)	7/8 (87.5%)	6/8 (75%)	20/24 (83.3%)
Combined Groups	13/14 (92.9%)	13/14 (92.9%)	6/8 (75%)	32/36 (88.9%)

Data presented as number and % of Efficacy Evaluable subjects who received or did not receive midazolam for sedation during the DEX infusion within each dose level by Age Group.
Age Group I = ≥ 28 to < 36 weeks gestational age; Age Group II = ≥ 36 to ≤ 44 weeks gestational age.
N = number of Efficacy Evaluable subjects at given Dose Level.
Dose Level 1 is 0.05 mcg/kg loading dose, 0.05 mcg/kg/hour maintenance dose.
Dose Level 2 is 0.1 mcg/kg loading dose, 0.1 mcg/kg/hour maintenance dose.
Dose Level 3 is 0.2 mcg/kg loading dose, 0.2 mcg/kg/hour maintenance dose.
Source: DEX-09-08 Interim Study Report, Table 14.2.1.1; DEX-09-08 Addendum to the Interim Study Report, Table 14.2.1; Data on File WW SEP2012.

Source: 2.7.3 Summary of Clinical Efficacy, pg 25

DEX-11-06 was a Phase II/III, open-label, multicenter, safety and efficacy study of DEX administered as an intravenous (IV) loading dose followed by a continuous IV infusion in preterm neonates ≥ 28 weeks to < 36 weeks gestational age who were initially intubated and mechanically ventilated. Subjects were in an intensive care setting and anticipated to require a minimum of 6 hours of continuous IV sedation. Subjects were administered a 10-to 20-minute loading dose of DEX followed by a maintenance dose of DEX for a minimum of 6 hours and up to a maximum of 24 hours. A total of 6 subjects received DEX and completed the treatment. The primary efficacy end point was the percentage of subjects who received rescue midazolam for sedation during the DEX infusion while intubated. None of the 6 subjects (0%) received rescue midazolam for sedation during the DEX infusion while intubated. DEX at a dose of 0.2 mcg/kg loading dose/0.2 mcg/kg/hr maintenance dose was effective at sedating critically ill, initially intubated and mechanically ventilated premature infants ≥ 28 to < 36 weeks gestational age.

4.1.2 Supportive studies

Three supportive safety/pharmacokinetic/pharmacodynamic studies, CHOP, DEX-08-01, and DEX-11-01 were conducted by Hospira.

The *CHOP study* was an open label study that enrolled subjects from 1 month of age to 2 years of age. The intent of the study was to investigate PK/PD of LD and MD of DEX for sedation in pediatric subjects post-op from cardiac surgery with tracheal intubation/ mechanical ventilation. The primary efficacy parameter was the percent of subjects not requiring rescue midazolam. 100% of subjects receiving Dose Level 1, 88.9% of subjects receiving Dose level 2, and 63.6% of subjects receiving Dose Level 3 did not require midazolam. For subjects who received midazolam, the one subject in Dose Level 2 received 6.1 mg, and the 4 subjects in Dose Level 3 received a median dose of 0.55 mg. In the combined Age Groups, the time to successful extubation was 5.9 hours for Dose Level 1, 4.8 hours for Dose Level 2, and 3.3 hours for Dose Level 3. The results of the study are presented in the table below.

Table 5. Efficacy results for the CHOP Study

	Dose Level 1 (N = 9)	Dose Level 2 (N = 9)	Dose Level 3 (N = 11)
Number and Percent of Subjects Not Requiring Midazolam			
Combined Age Groups	9/9 (100.0%)	8/9 (88.9%)	7/11 (63.6%)
Median Dose of Rescue Midazolam [1] (mg)			
Combined Age Groups	N/A	6.1	0.55
Kaplan-Meier Estimates of Time to Successful Extubation (hours)			
Combined Age Groups	5.9	4.8	3.3

N = Number of subjects in the Efficacy Evaluable Population at the given Dose Level.
Dose Level 1: loading dose 0.35 mcg/kg; maintenance dose 0.25 mcg/kg/hr.
Dose Level 2: loading dose 0.70 mcg/kg; maintenance dose 0.50 mcg/kg/hr.
Dose Level 3: loading dose 1.0 mcg/kg; maintenance dose 0.75 mcg/kg/hr.
For subjects who received rescue midazolam.
Abbreviations: hr = hour; kg = kilogram; mcg = microgram; mg = milligram; N/A = not applicable.
Source: End-of-Text Table 10.1.2, End-of-Text Table 13.1.2.

Source: Clinical Overview, pg 27

For *study DEX-08-01*, which enrolled subjects 2 to < 17 years of age, the results of the primary efficacy analysis is provided in the table below. The efficacy parameters included percent of subjects not requiring rescue midazolam for sedation, median dose of midazolam received for those subjects requiring rescue, and the time to successful extubation. 57.1% of subjects receiving Dose Level 1, 53.8% of subjects receiving Dose level 2, 64.3% of subjects receiving Dose Level 3, and 78.6% of subjects receiving Dose Level 4 did not require midazolam. For subjects who received midazolam, the median doses received by the six combined Age Group subjects in Dose Level 1, the six combined Age Group subjects in Dose Level 2, the 5 combined Age Group subjects in Dose Level 3 and the 3 combined Age Group subjects in Dose Level 4 were 2.84 mg, 1.75 mg, 6.00 mg, and 3.96 mg, respectively.

Table 6. Efficacy results for Study DEX-08-01

	Dose Level 1 (N = 9)	Dose Level 2 (N = 9)	Dose Level 3 (N = 11)
Number and Percent of Subjects Not Requiring Midazolam			
Combined Age Groups	9/9 (100.0%)	8/9 (88.9%)	7/11 (63.6%)
Median Dose of Rescue Midazolam [1] (mg)			
Combined Age Groups	N/A	6.1	0.55
Kaplan-Meier Estimates of Time to Successful Extubation (hours)			
Combined Age Groups	5.9	4.8	3.3

N = Number of subjects in the Efficacy Evaluable Population at the given Dose Level.
Dose Level 1: loading dose 0.35 mcg/kg; maintenance dose 0.25 mcg/kg/hr.
Dose Level 2: loading dose 0.70 mcg/kg; maintenance dose 0.50 mcg/kg/hr.
Dose Level 3: loading dose 1.0 mcg/kg; maintenance dose 0.75 mcg/kg/hr.
For subjects who received rescue midazolam.
Abbreviations: hr = hour; kg = kilogram; mcg = microgram; mg = milligram; N/A = not applicable.
Source: End-of-Text Table 10.1.2, End-of-Text Table 13.1.2.

Source: Clinical Overview, pg 28

The review of efficacy and safety is evaluated in the medical and statistical reviews.

4.1.3 Population Pharmacokinetic Evaluation of Dexmedetomidine Infusion in Mechanically Ventilated Pediatric Subjects

The objectives of the analyses were to conduct an exploratory graphical review of the DEX PK data from the CHOP (Children's Hospital of Philadelphia) study, Study DEX-08-01, Study DEX-09-08, and Study DEX-11-01 in order to characterize the PK. A PK model was developed to describe the PK disposition of DEX in pediatric subjects (including neonates) and assess the influence of demographic covariates and concomitant medications on the variability in the model parameters.

4.1.3.1 Data

Data for this analysis were obtained from 4 clinical trials. The CHOP study was a Phase 2, single center, open-label, dose escalation study of the PK and pharmacodynamics (PD) of DEX in infants postoperative from cardiac surgery. Study DEX-08-01 was a Phase 2, multicenter, open-label, dose escalation study of the PK and PD of DEX in children and adolescents in an intensive care setting. Study DEX-09-08 was a Phase 2/3, multicenter, open-label study of the PK, safety, and efficacy of DEX in neonates in an intensive care setting. Study DEX-11-01 was a Phase 2, randomized, open-label, PK and PD study of DEX in pediatric subjects aged 12 months through <24 months. The dosing, number of subjects and number of plasma concentrations available for the analysis are presented in the table below.

Table 7. Dosing and PK information used for Population PK modeling of DEX

Study	Dexmedetomidine Treatment Group (Loading Dose + Maintenance Infusion Rate)	Number of Subjects	Number of Concentrations
DEX-09-08	0.05 mcg/kg + 0.05 mcg/kg/h	10	63
	0.10 mcg/kg + 0.10 mcg/kg/h	14	88
	0.20 mcg/kg + 0.20 mcg/kg/h	8	55
Subtotals for DEX-09-08		32	206
CHOP	0.35 mcg/kg + 0.25 mcg/kg/h	12	139
	0.70 mcg/kg + 0.50 mcg/kg/h	12	152
	1.00 mcg/kg + 0.75 mcg/kg/h	12	152
Subtotals for CHOP		36	443
DEX-08-01	0.25 mcg/kg + 0.20 mcg/kg/h	15	169
	0.50 mcg/kg + 0.40 mcg/kg/h	14	159
	1.00 mcg/kg + 0.70 mcg/kg/h	15	167
	1.00 mcg/kg + 2.00 mcg/kg/h	14	168
Subtotals for DEX-08-01		58	663
DEX-11-01	0.70 mcg/kg + 0.50 mcg/kg/h	2	24
	1.00 mcg/kg + 0.75 mcg/kg/h	3	36
Subtotals for DEX-11-01		5	60
Overall		131	1372

Source: DEX-PK-Modeling Report, pg 50

Rich PK sampling was performed according to similar schedules in the CHOP study, Study DEX-08-01, and Study DEX-11-01. In these studies, blood was drawn prior to the loading dose, at 5 times during the maintenance infusion (0.5, 1, 2, and 4 - 6 h after the start plus 1 sample near the end of the infusion) and at 0.25, 0.5, 1, 2, 4, 8, 12, and 15 - 18 h after the end of the maintenance infusion in the CHOP study and at 10 min, 0.5, 1, 2, 4, and 10 h after the end of the maintenance infusion in Study DEX-08-01 and Study DEX-11-01.

4.1.3.2 Methods

Population PK modeling was performed using NONMEM 6.2. First-order conditional estimation (FOCE) with interaction method was used at all stages of model development. The effects of both weight and age were included in the model considered the base structural model, given the range of weights and ages in this pediatric population and the likely impact on PK.

Evaluation of the influence of other covariates (sex, ethnicity, cardio-pulmonary bypass use, albumin infusion, and site of sampling on elimination clearance (CL) and volume of the central compartment (Vc); alanine aminotransferase (ALT), total bilirubin, concomitant glucuronidation pathway inhibitors, and heart physiology (single versus double ventricle) on CL) was performed using a forward selection ($\alpha = 0.05$ plus at least a 5% reduction in interindividual variability (IIV) in the parameter of interest) followed by a backward elimination ($\alpha = 0.001$) procedure.

Adequacy of the final model was evaluated using a simulation-based prediction-corrected visual predictive check method. Conditional on the final model point estimates, 1000 replicates of the analysis dataset were simulated using NONMEM, and the 5th, 50^{th} (median), and 95th percentiles of the distributions of the simulated concentrations were calculated. Concordance between the prediction interval based on the simulations and the observed data and corresponding percentiles of the observed data was assessed visually and numerically, by calculating the percentage of observed data points above and below the prediction interval bounds.

Using the final population PK model for DEX, 95% confidence intervals about the geometric mean of the empirical Bayesian estimates of clearance (CL) and volume of the central compartment (Vc) were calculated, applying a correction factor to inflate the standard deviations of logCL and logVc based on the observed shrinkage in the estimates. The lower and upper bounds of the confidence intervals were also expressed relative to the point estimates and compared to the targeted bounds of 0.6 to 1.4.

4.1.3.3 Results

The base structural model for the pooled dataset of Study DEX-09-08, CHOP study, Study DEX-08-01, and Study DEX-11-01 was a 2-compartment model with fixed allometric exponents for weight effects on clearance and volume parameters (0.75 for CL and intercompartmental clearance (Q) and 1.0 for Vc and volume of the peripheral compartment (Vp)), an additional shift in the CL and Vc exponents for neonates, and age effects on Q and Vp described by power functions (both decrease with increasing age).

No additional covariate effects were added to the model as none met the pre-specified criteria of a statistically significant reduction in the MVOF and at least a 5% decrease in IIV. During

subsequent model refinement, the shift in the Vc allometric exponent for neonates was found to be non-statistically significant and was thus removed from the model.

The final base structural PK model was a 2-compartment model with IIV estimated on CL, Q, Vc, and Vp using exponential error models, fixed allometric exponents on the clearance (0.75 for CL and Q) and volume of distribution (1.0 for Vc and Vp) parameters, with an additional shift on the CL exponent for neonates, age effects on Q and Vp described by power functions (both decrease with increasing age), covariance terms for the IIVs on CL and Vp, and the IIVs on Q and Vc, separate additive plus constant coefficient of variation error models for Studies DEX-08-01 and CHOP, and a constant coefficient of variation error model for Studies DEX-09-08 and DEX-11-01.

The parameter estimates from the final PK model are presented in the Table 8 below and the goodness-of-fit plots are presented in Figure 6, with Visual Predictive Check presented in Figure 7.

Table 8. Parameter Estimates from the Final Population PK Model for DEX

	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
Parameter	Population Mean	%SEM	Final Estimate	%SEM
CL (L/h)[a]	10.7	3.4	37.01	17.0
Proportional shift in allometric exponent for CL for neonates[a]	0.531	17.2		
Vc (L)[b]	8.49	10.5	53.76	20.8
Intercompartmental CL (L/h)[c]	63.5	23.8	161.25	23.7
Exponent for power function effect of age on Q[c]	-0.342	27.9		
Vp (L)[d]	14.7	7.2	51.19	20.6
Exponent for power function effect of age on Vp[d]	-0.280	10.6		
Ratio of additive to proportional RV: CHOP	12.3	15.0	NA	NA
Ratio of additive to proportional RV: DEX-08-01	40.4	26.0	NA	NA
cov(IIV in CL, IIV in Vp)	0.145	20.8	NA	NA
cov(IIV in Q, IIV in Vc)	0.796	19.6	NA	NA
RV DEX-09-08[e]	0.189	18.6	NA	NA
RV CHOP[f]	0.0358	16.5	NA	NA
RV DEX-08-01[g]	0.0685	20.6	NA	NA
RV DEX-11-01[h]	0.0935	29.8	NA	NA
Minimum value of the objective function = 11885.512				

Abbreviations: CHOP, Children's Hospital of Philadelphia; CL, elimination clearance; IIV, interindividual variability; NA, not applicable; NEO, indicator variable for neonates; %CV, coefficient of variation expressed as a percentage; %SEM, standard error of the mean expressed as a percentage; Q, intercompartmental clearance; RV, residual variability; Vc, volume of the central compartment; Vp, volume of the peripheral compartment; WTKG, weight in kg.

Source: DEX-PK-Modeling Report, pg 9

The equations describing the relationships between the typical DEX parameter values and the subject factors included in the model (that is, those relating to weight and age) are provided below.

$$Typical\ CL_j = 10.7 \times \left(\frac{WTKG_j}{9.6}\right)^{[0.75 \times (1 + 0.531 \times NEO_j)]}$$

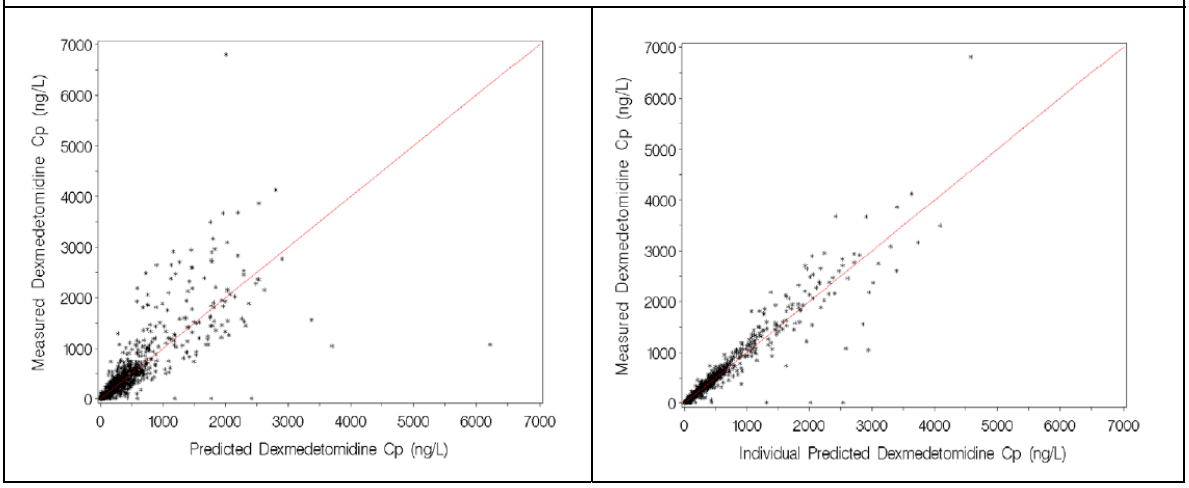
$$Typical\ Vc_j = 8.49 \times \left(\frac{WTKG_j}{9.6}\right)$$

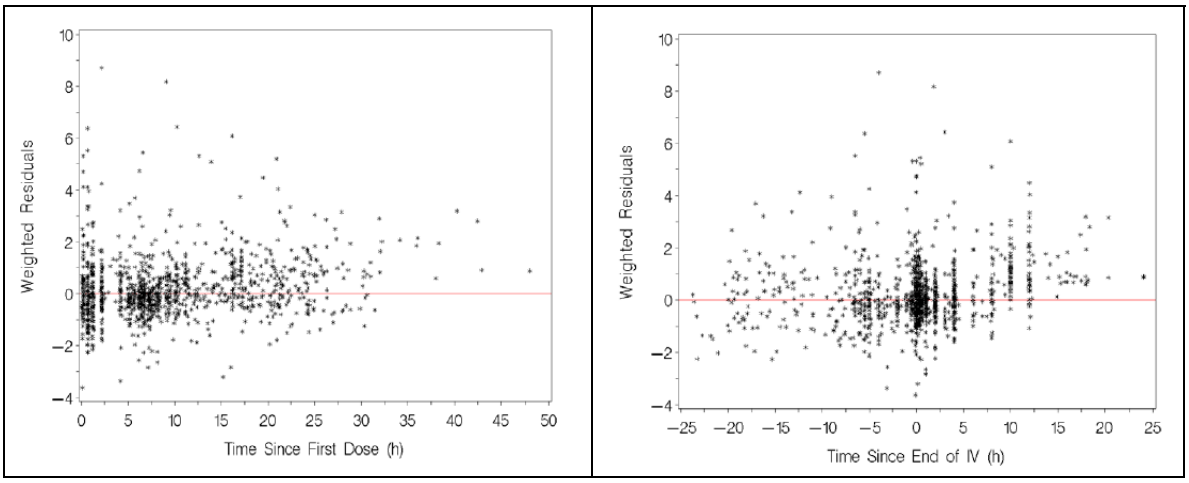
$$Typical\ Q_j = 63.5 \times \left(\frac{WTKG_j}{9.6}\right)^{0.75} \times \left(\frac{age_j}{1.31}\right)^{-0.342}$$

$$Typical\ Vp_j = 14.7 \times \left(\frac{WTKG_j}{9.6}\right) \times \left(\frac{age_j}{1.31}\right)^{-0.280}$$

Where: *CLj* is the typical value of DEX clearance in the *j*th subject, *Vcj* is the typical value of DEX volume of the central compartment in the *j*th subject, *Qj* is the typical value of DEX intercompartmental clearance in the *j*th subject, *Vpj* is the typical value of DEX volume of the peripheral compartment in the *j*th subject, age *j* is the age, in years, of the *j*th subject, *WTKGj* is the weight, in kg, of the *j*th subject, and *NEOj* is an indicator variable with a value of 1 for neonate subjects and 0 otherwise.

Figure 6. Goodness of fit plots for the final population PK model for DEX

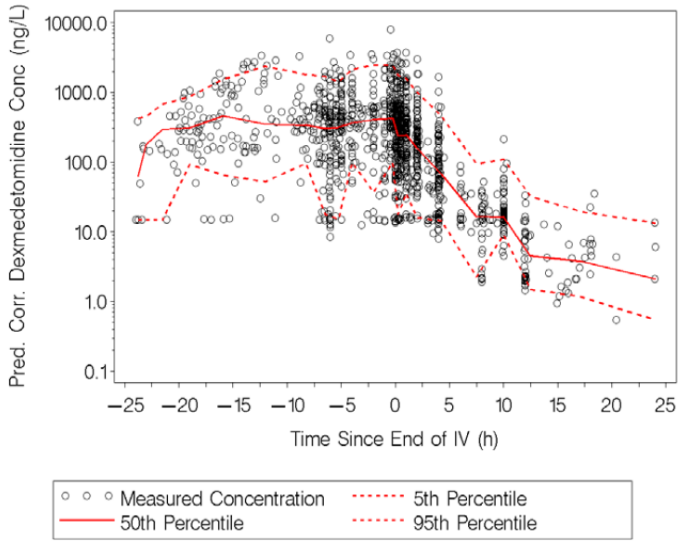




Source: DEX-PK-Modeling Report, pg 83-84

The majority of the observed data falls within the prediction interval. The percentage of the observed concentrations below the 5th percentile was 6.5% and the percentage above the 95th percentiles was 4.5%.

Figure 7. Visual-Predictive Check for DEX PK Model – Prediction Interval Overlaid on Observed Data



Source: DEX-PK-Modeling Report, pg 87

This pediatric PK model can be further used to extrapolate values for pediatric PK parameters to values expected at usual adult ages and weights, for comparison to typical PK parameter values obtained from the previously developed adult population PK model for DEX. Based on a hypothetical pediatric subject at the upper end of the ranges for age and weight (that is, 17 years

and 70 kg), the DEX CL and volume of distribution are predicted to be 47.5 L/h and 114.2 L, compared to corresponding values of 39 L/h (mean body weight associated with this CL was 72 kg) and 118 L as reported in the product label for Precedex, 35.8 L/h and 112.7 L in the typical subject from the adult population PK analysis of long-term (> 24 h) DEX use, and 39.4 L/h and 152 L, respectively, from the non-compartmental analysis of this data.

4.1.3.4 Sponsor's Conclusions

Overall, this model provides a robust characterization of the PK of DEX in pediatrics. The model evaluation results provide evidence that the model is able to predict well over the entire range of DEX concentrations occurring during the maintenance infusion, as well as after discontinuation. Estimated parameters for DEX CL and Vc achieved the targeted levels of precision. In addition, this population model is based on the largest population of pediatric subjects, and broadest range of ages (neonate to 17 years), maintenance doses, and infusion durations reported to date.

- A linear 2-compartment model was found to best characterize the pooled DEX concentration data collected from pediatric subjects enrolled in 4 studies after different dosing regimens.
- 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 subjects.
- 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- versus double-ventricle), use of concomitant glucuronidation pathway inhibitors, albumin infusion, use of cardio-pulmonary 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.

Reviewer's comments: *An analysis assessing the PK characteristics of DEX in a pediatric population was performed using population PK methodology. PK information included rich sampling data available from four PK studies performed in a patient population of n=131 subjects (age range from neonates to 17 years). Various loading and maintenance doses were*

employed to assess the PK of DEX in the pediatric population. The reviewer believes the amount of information used to inform the PK model is adequate.

All fixed and random effect parameters were estimated with good precision (%SEMs < 30%). Residual diagnostics and goodness of fit plots based on the sponsor's analyses showed that the model fitted the data reasonably well. Moreover, the VPC indicates no apparent biases in the overall model fit by comparing the simulated data (based on the model) to the raw data.

With regard to the covariates chosen, the reviewer's independent analysis resulted in similar results with similar parameter estimates. Therefore, the reviewer concludes the analysis, and the corresponding conclusions and interpretations, presented by the sponsor is reasonable. The reviewer performed an independent analysis to assess the precision of the parameter estimates for different age groups.

5 Reviewer's Analysis

5.1 Objectives

Analysis objectives are:

1. To evaluate the population PK model and determine the precision of the PK parameter estimates for the different pediatric age groups.
2. Assess is cardiopulmonary bypass (CPB) has an influence on the exposure of DEX.
3. Determine if an exposure-response relationship exists for DEX.

5.2 Methods

An assessment of the population PK model was conducted by re-analysis of the submitted sponsor PK data. Using the final population PK model for DEX, 95% confidence intervals about the geometric mean of the empirical Bayesian estimates of clearance (CL) and volume of the central compartment (Vc) were calculated for each age group including the following categories: 28 weeks GA - < 1 month, 1 month - < 6 months, 6 months - < 12 months, 12 months - < 24 months, 2 years - < 6 years, and 6 years - < 17 years.

Based on diagnostic plot assessments, the reviewer concurred with the analysis presented by the sponsor. A representative example of individual plots is presented in Figure 8. Similar diagnostics to the sponsor's presented plots were observed with the reviewer's analysis. A comparison of the weight-adjusted clearance and central volume of distribution, by the six different age groups, is presented in Figure 9. The weight-adjusted volume shown indicates that the volume, when corrected for body weight, remains relatively constant with increasing age. There was a lower weight-adjusted clearance observed in neonates compared to infants which may be attributed to a lack of maturation of clearance mechanisms in neonates.

Figure 8. Individual plots with observed (grey circles), individual prediction (red lines and population prediction (blue dashed line).

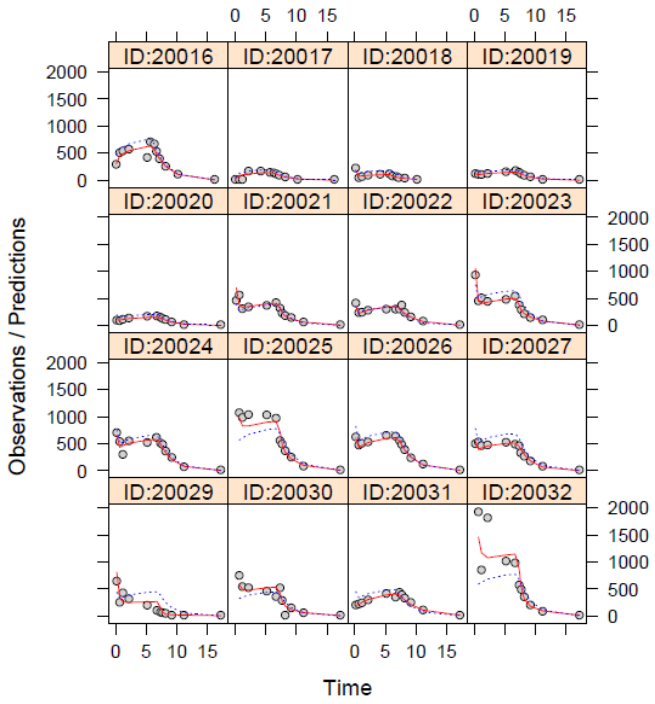
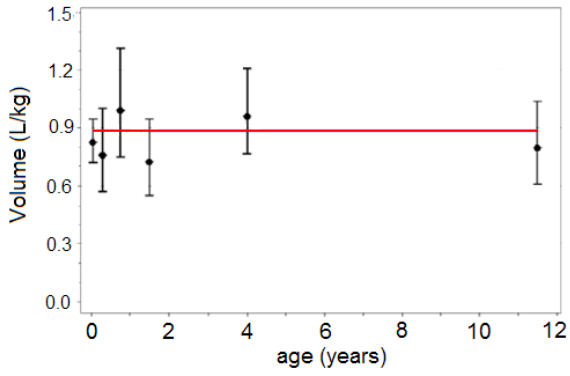
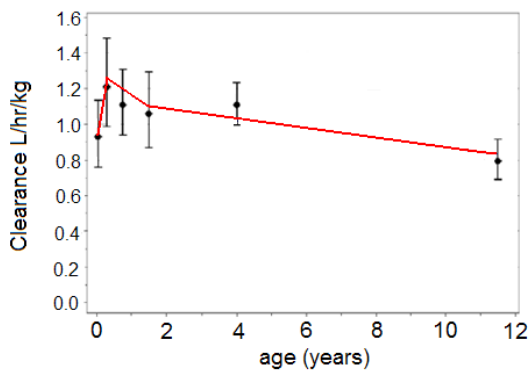


Figure 9. Geometric means and 95% CI for the Estimates of DEX weight-adjusted Volume of the Central Compartment (left plot) and weight-adjusted Clearance (right plot) in the Specified age groups. Population model-based typical values are depicted as a red solid line.



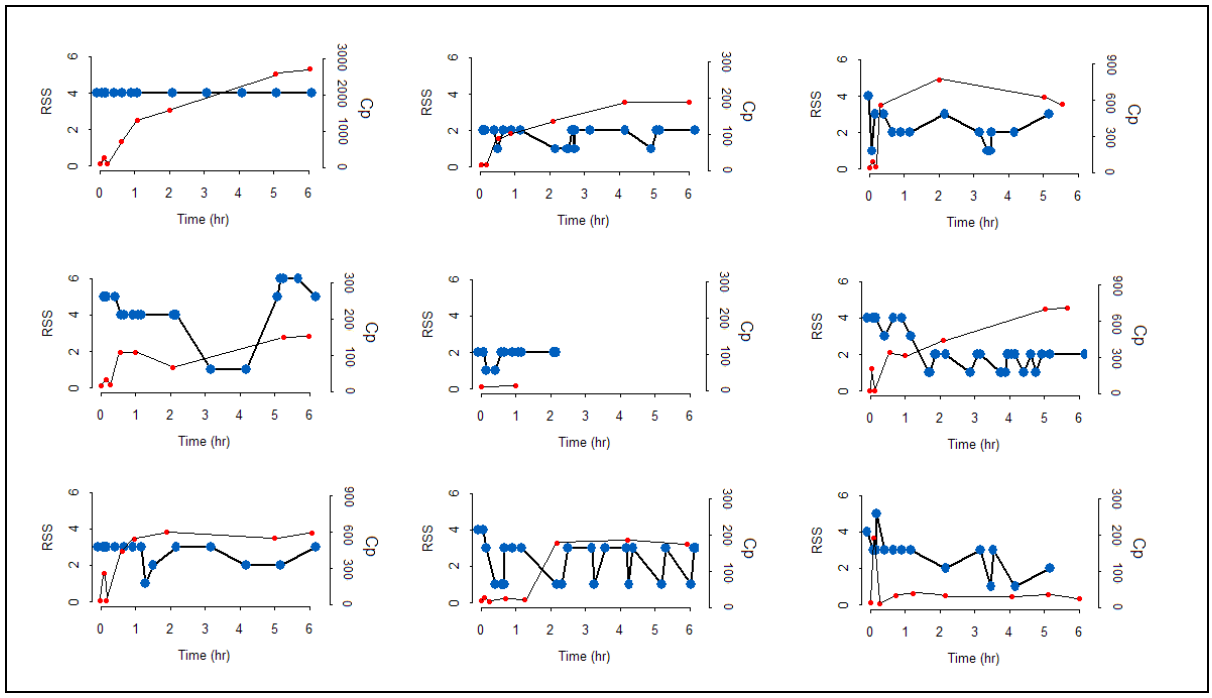


Further evaluation of the precision of the PK parameter estimates was performed. Using the final population PK model for DEX, 95% confidence intervals for the geometric mean of the empirical Bayesian estimates of clearance and volume of the central compartment were calculated. The geometric means, and corresponding relative precision (95% CI) for the PK parameters, by age group is presented in **Table 9**.

Table 9. Summary Statistics for the Geometric Mean Point Estimates and 95% CI of DEX Weight-Adjusted Volume and Clearance by Age Group (n= number of subjects in each age group from the database)

Age bracket (n)	*Volume (L/kg) 95%CI*	*Clearance (L/h/kg) 95%CI*
28 weeks GA - < 1 month (n=28)	0.83 (0.72, 1.15)	0.93 (0.82, 1.22)
1 month - < 6 months (n=14)	0.76 (0.76, 1.32)	1.21 (0.82, 1.23)
6 months - < 12 months (n=15)	0.99 (0.76, 1.32)	1.11 (0.85, 1.18)
12 months - < 24 months (n=13)	0.72 (0.76, 1.31)	1.06 (0.82, 1.22)
2 years - < 6 years (n=26)	0.96 (0.79, 1.26)	1.11 (0.9, 1.11)
6 years - < 17 years (n=28)	0.80 (0.76, 1.31)	0.80 (0.87, 1.15)

Figure 10. Individual plots of concentration (small red dots) and RSS (large blue dots) as a function of time for Study DEX-08-01.



Analysis of the influence on CPB on DEX clearance as well as the exposure-response assessment is presented is Section 1 of this document.

5.2.1 Data Sets

Data sets used are summarized in Table 10.

Table 10. Analysis Data Sets

Study Number(s)	Name	Link to EDR
Pooled PK data or population analysis	pk4stdy.xpt	\\cdsesub1\evsprod\NDA021038\0022\m5\datasets\dex-pk-modeling\analysis
DEX-08-01	adrs.xpt, adsl.xpt, dm.xpt, rs.xpt, ra.xpt	\\cdsesub1\evsprod\NDA021038\0022\m5\datasets\dex-08-01\tabulations

5.2.2 Software

TIBCO Spotfire S-PLUS 8.0 was used for data organization, as well as graphical and statistical analysis.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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05/23/2013

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