13 December 2012
EMA/145296/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dexdor

International non-proprietary name: DEXMEDETOMIDINE

Procedure No. EMEA/H/C/002268/II/0003

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Dexmedetomidine (Dexdor) is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasised. Dexmedetomidine is relatively free from respiratory depressive effects.

Dexdor is indicated for the sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3). It is presented as 100 µg /ml concentrate for solution for infusion. The recommended dose is an initial infusion rate of 0.7 µg /kg/h which may then be adjusted stepwise within the dose range 0.2 to 1.4 µg /kg/h in order to achieve the desired level of sedation.

This variation refers to an update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to revise the paediatric information based on the results of new paediatric studies submitted in accordance with article 46 of the Paediatric Regulation. Linguistic changes are made in the following countries: Greece, France, Italy, Czech Republic.

1.2. Clinical aspects

The limited paediatric information reflected in the current SmPC (sections 4.2, 4.8, 5.1 and 5.2) is based on the following studies, previously submitted at the time of the initial marketing authorisation (MAA):

- **W98-266**: a pharmacokinetic/pharmacodynamic (PK/PD) study in 36 subjects aged 2-12 years who received 2- 6 µg/kg/hr dexmedetomidine for 10 minutes pre-operatively;
- **2004-5-3770**: a PK/PD study in 38 subjects aged 1 month to 2 years who received a loading dose then maintenance doses of dexmedetomidine 0.25- 0.75 µg/kg/hr for up to 24 hours in the paediatric ICU;
- **DEX-08-01**: a phase II study of safety and efficacy in 59 ICU subjects aged between 2 and 17 years who received dexmedetomidine 0.2-2 µg/kg/hr (plus loading dose) for up to 24 hours.

It is known from the previously submitted data that dexmedetomidine exposure in children 2.3 to 11.5 years of age appeared to be somewhat lower than in adults receiving the same body weight-adjusted regimen as a result of higher body weight-adjusted clearance in children. In Study W98-266 a single i.v. dose of dexmedetomidine was administered to 36 children across three dosing groups for 10 minutes: 2.0 µg/kg/h Group I; 4.0 µg/kg/h Group II; and 6.0 µg/kg/h Group III. Pharmacokinetic results are presented in Table 1:

Table 1. Pharmacokinetic results – Study W98-266

Pharmacokinetic Parameters	2.0 µg/kg/h Dose Group	4.0 µg/kg/h Dose Group	6.0 µg/kg/h Dose Group
N	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
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

However, data from studies with children less than 2 years are not consistent. In one study where dexmedetomidine was administered to post-operative, cardiac surgical infants (aged 1 month to 2 years) no apparent change in clearance and weight-adjusted clearance across the age range was observed (Study 2004-5-3770). In that study dexmedetomidine body weight-adjusted clearance values in infants were also higher than those reported in adults. Data from a third study suggests that children younger than one year of age might have lower bodyweight-adjusted clearances when compared to older children and adults (Potts AL et al., 2009, Potts AL et al., 2008) implying that higher steady-state dexmedetomidine plasma concentrations would be predicted when dosing in proportion to bodyweight.

Within this variation application, 3 new paediatric studies are being submitted in accordance with article 46 of the Paediatric Regulation and are as follows:
- **DEX-11-01**: A PK/PD study in 5 paediatric subjects aged 12-24 months, treated at 2 dose levels up to 0.75 µg/kg/hr for up to 24 hours in the ICU.
- **DEX-09-08**: A PK/PD study in neonates in the ICU patients. 36 patients were enrolled from 28-44 weeks gestational age to receive a loading dose then dexmedetomidine 0.05-0.2 µg/kg/hr for up to 24 hours;
- **DEX-08-05**: A phase III study of efficacy and safety of dexmedetomidine in 175 subjects in the ICU aged 1 month to 17 years, who received an optional loading dose then dexmedetomidine 0.2-1.4 µg/kg/hr for up to 24 hours;

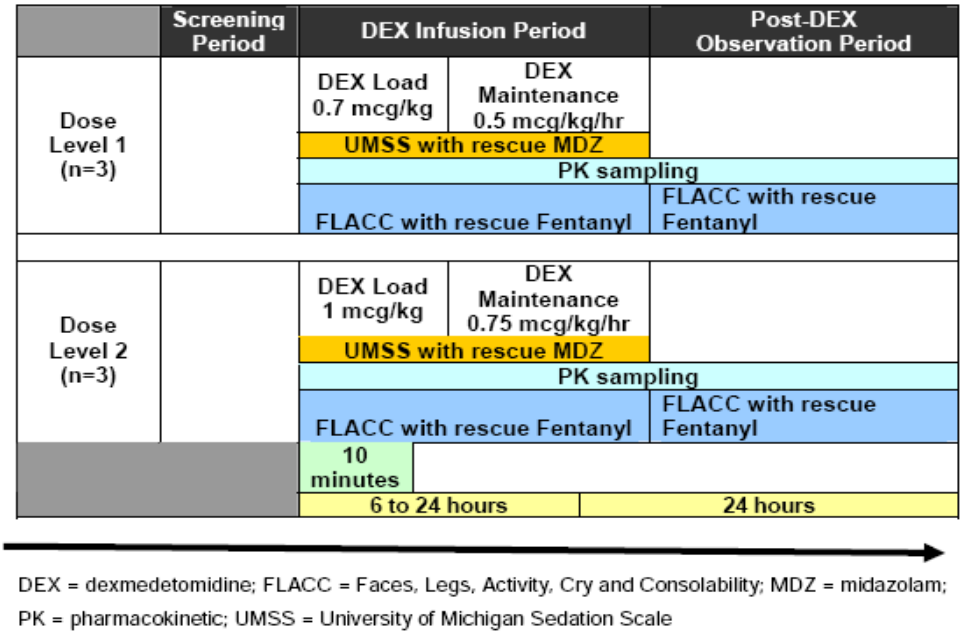
The CHMP also noted that the remaining paediatric data to be submitted relate to the final Pre-term group (6 subjects) from the DEX-09-08 study which will now be collected as a separate study. This study is in the set-up phase and results are not expected before the end of 2012.

1.2.1. Study DEX-11-01

This was a phase II, randomized, open-label, single centre, pharmacokinetic and pharmacodynamic study of dexmedetomidine in paediatric subjects aged 12 months to < 24 months. The objectives were: 1) To define the pharmacokinetic (PK) profile of dexmedetomidine (DEX) administered as an intravenous (IV) loading dose followed by a continuous IV infusion in paediatric subjects; 2) To define the pharmacodynamic (PD) profile of DEX administered as an IV loading dose followed by a continuous IV infusion in paediatric subjects

The study design is summarised in Figure 1.

Figure 1



DEX = dexmedetomidine; FLACC = Faces, Legs, Activity, Cry and Consolability; MDZ = midazolam; PK = pharmacokinetic; UMSS = University of Michigan Sedation Scale

1.2.1.1. Methodology

Study participants

Inclusion criteria

These were as follows: 1) Initially intubated and mechanically ventilated paediatric subjects (⩾12 months to <24 months) in an intensive care setting. The subject must have been mechanically ventilated prior to and during the commencement of study drug; 2) Anticipated to require a minimum of 6 hours of continuous IV sedation and 3) Subject had adequate renal function, defined as serum creatinine ≤ 1.0 mg/dL

Exclusion criteria

These were as follows: 1) Paediatric subjects with neurological conditions that prohibited an evaluation of sedation (e.g diminished consciousness from increased intracranial pressure, extensive brain surgery requiring intracranial pressure monitor), diminished cognitive function per investigator discretion; subjects with immobility from neuromuscular disease or continuous infusion of neuromuscular blocking (NMB) agents); 2) Subjects with second degree or third degree heart block unless the subject had a permanent pacemaker or pacing wires were in situ; 3) Subjects who had hepatic impairment as defined by a serum glutamic-pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT) > 90 U/L at the time of screening; 4) Subjects who had hypotension, based on repeat assessments within 15 minutes preceding the start of DEX, defined as Systolic Blood Pressure (SBP) < 70 mmHg; 5) Pre-existing bradycardia based on repeated assessments within 15 minutes preceding the start of DEX, defined as Heart rate (HR) < 70 bpm; 6) Subjects who had acute thermal burns involving more than 15% total body surface area; 7) Subjects who had a known allergy to DEX, MDZ or fentanyl; 8) Subjects who had received DEX within 15 hours prior to the start of study drug; 9) Subjects with a life expectancy that was < 72 hours; 10) Subjects who were expected to have hemodialysis (continuous hemofiltration), peritoneal dialysis, or extracorporeal membrane oxygenation treatments within 48 hours prior to the start of DEX or during the duration of the study; 11) Subjects who had been treated with alpha-2 agonists/antagonists within 2 weeks ; 12) Subjects with a spinal

cord injury above T5; 13) Subjects who had received another investigational drug as part of an investigational drug study within the past 30 days; and 14) Subjects who, in the opinion of the investigator, might not have been able to comply with the safety monitoring requirements of this clinical study.

Treatments

Following completion of screening procedures, the DEX infusion began after discontinuation of all other sedative agents and after the subject had attained a University of Michigan Sedation Scale (UMSS) score ≤ 4. Subjects were randomly assigned into 1 of 2 dose levels: dose level 1 consisted of a 0.7 mcg/kg loading dose immediately followed by a 0.5 mcg/kg/hr maintenance infusion; dose level 2 consisted of a 1 mcg/kg loading dose immediately followed by a 0.75 mcg/kg/hr maintenance infusion. The DEX infusion (10 – minute loading dose and continuous fixed maintenance dose) continued for a minimum of 6 hours but did not exceed 24 hours, including the loading dose time. Titration of dosing was not allowed.

If the subject was not adequately sedated as defined by a UMSS score of 2 to 4; rescue medication (midazolam: MDZ) was administered as needed for sedation during DEX administration based on results of the UMSS scale and investigator judgment. Similarly rescue opiate analgesia, consisting of IV fentanyl was administered, based on the judgment of the investigator or designee, or when the FLACC (Faces, Legs, Activity, Cry and Consolability) score was > 4.

Outcomes/endpoints

Pharmacokinetics

The PK parameters included: AUC (area under the plasma concentration-time curve), Cmax (observed peak plasma concentration), CL (plasma clearance), t1/2 (terminal half-life), Vd (volume of distribution). Venous blood samples of 1ml were collected at the following timepoints: no more than 30 minutes prior to start of the loading dose; within 5 minutes before finishing the loading dose; 30 minutes, 1, 2 and 4-6 hours after start of maintenance infusion; within 30 minutes prior to end of maintenance infusion (must be within 24 hours of start of maintenance infusion); 10 minutes after end of maintenance infusion, and 30 minutes, 1, 2, 4, and 10 hours after end of maintenance infusion.

Pharmacodynamics

1) Whenever possible, the same investigator or designee obtained UMSS scores according to the following schedule: just prior to loading dose, and then at 5 and 10 minutes during loading dose; at the start of maintenance of infusion, and at 5, 10, 15, 30, and 60 minutes for the first hour; every 4 hours thereafter during the remainder of the maintenance infusion; within 5 minutes of obtaining each PK sample; if rescue medication was given, UMSS measurements were obtained before and within 5 minutes after any MDZ rescue administration during DEX infusion period.

2) The pain assessments were collected according to the following schedule: immediately prior to the loading dose; hourly during the maintenance infusion; within 5 minutes after any fentanyl bolus administered for pain during DEX infusion or every 4 hours if receiving a continuous infusion of fentanyl. If on a continuous infusion of fentanyl, and the drug was titrated, FLACC assessments were collected within 5 minutes prior to and within 5 minutes following titration.

Statistical Methods

The full evaluable (FE) population consisted of all subjects who received study drug for at least 5 hours with adequate PK samples. The safety evaluable (SE) population consisted of all subjects who received any amount of study drug. It was stated that descriptive statistics only were planned for all analyses, both PK and PD, because of the small sample size (only 3 subjects per dose), although non-significant p-values were supplied for the analysis of time to successful extubation and time to rescue medication (using the log-rank and Wilcoxon tests). The choice of sample size was not based on statistical considerations.

1.2.1.2. Results

Recruitment / Number analysed

A total of 5 subjects were randomized at one site in the United States (US). Two subjects were randomized to dose level 1 and 3 subjects to dose level 2. There were no drop-outs and the evaluable population was the same as the safety population. Two female and three male patients were enrolled. Four subjects were white and 1 subject declined specification of race. One female was randomised to each dose group. One boy was randomised to the lower dose group and two to the higher group.

Patient characteristics

The mean age was 17.30 months (range 14.60 – 21.20). The mean height and weight were similar for dose levels 1 and 2 (73.75 and 76.17 cm; 10.04 and 10.50 kg, respectively). The height ranged from 72.5cm to 82.0cm and weight 8.9kg to 13.5kg. The most common medical history included cardiovascular and respiratory disease in all 5 subjects. Four of the five subjects had gastrointestinal conditions. All subjects were post-surgery.

Pharmacokinetics

Table 2. pharmacokinetic results

Pharmacokinetic Parameter (units)	Dose Level 1 DEX LD=0.7 mcg/kg MD=0.5 mcg/kg/hr (N = 2) Mean (%CV)	Dose Level 2 DEX LD=1 mcg/kg MD=0.75 mcg/kg/hr (N = 3) Mean (%CV)
CL (L/hr)	12.192 (78.55)	5.836 (50.30)
CL_w (L/hr/kg)	1.292 (87.48)	0.617 (61.79)
AUC (0-Infinity) [(pg/mL)hr]	4639.170 (87.48)	14203.544 (91.89)
$AUC\ (0\text{-}Infinity)_{Dose}$ [(pg/mL)hr/mcg]	118.610 (78.55)	221.131 (67.92)
C_{max} (pg/mL)	4499.925 (129.49)	11737.387 (30.24)
V_d (L)	31.845 (64.17)	15.780 (22.47)
V_{dw} (L/kg)	3.343 (74.52)	1.590 (39.01)
$t_{1/2}$ (hr)	1.958 (19.22)	2.260 (53.99)
CV=coefficient of variation; LD=Loading dose; MD=maintenance dosing Source: Table 14.2.7.1		

Pharmacodynamics

Two subjects (40.0%) received rescue MDZ for sedation during DEX infusion: 1 (50%) subject in dose level 1 and 1 (33.3%) in dose level 2. Three subjects (60.0%) received rescue fentanyl for analgesia during DEX infusion: 1 (50.0%) subject in dose level 1 and 2 (66.7%). subjects in dose level 2. No observations were made regarding the time to first dose of rescue medication due to the small number of subjects.

For dose levels 1 and 2, the median absolute time spent in the UMSS score between 2 and 4 (target level of sedation) was 3.6 hours (58.9% of the time) and 5.9 hours (95.1% of the time), respectively. The median absolute time spent with a total UMSS score < 2 for dose levels 1 and 2 was 2.5 hours (41.1% of the time) and 0.3 hours (4.9%), respectively. The median total FLACC score was 1.6 in dose level 1 and 4.4 in dose level 2, and 3.2 for both dose levels combined. However, these results were confounded by administration of concomitant sedative/analgesic drugs during DEX infusion as detailed above.

Safety

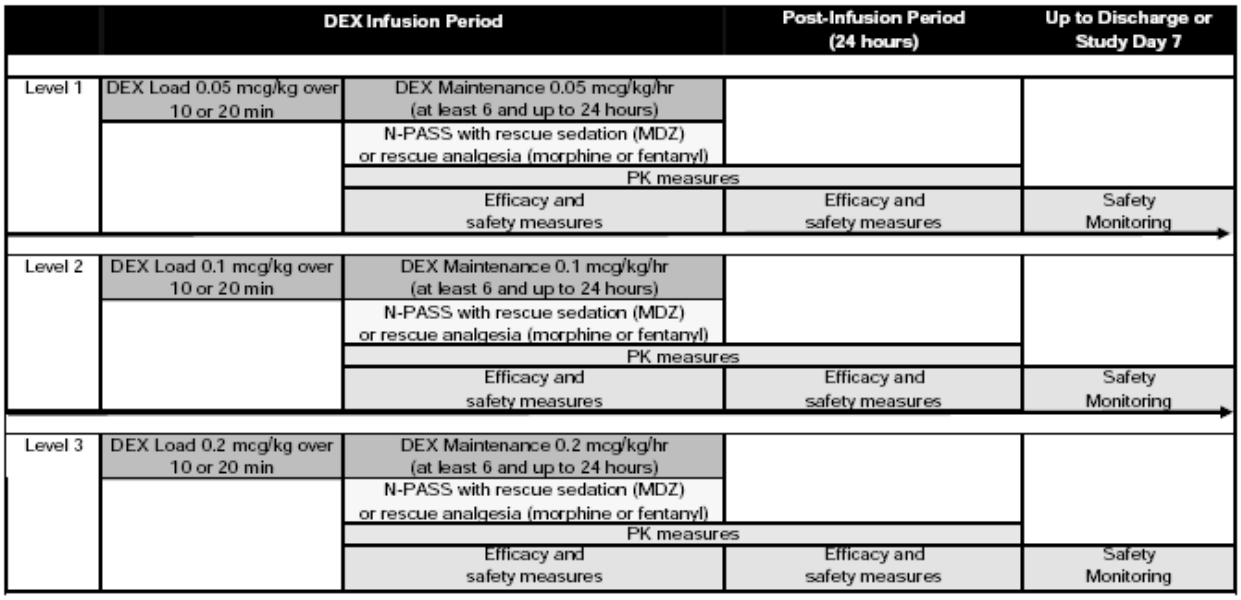
Only 1 of the 5 subjects (20.0%) experienced treatment emergent adverse events (TEAEs). These events were mild pyrexia and mild atelectasis in a dose level 2 subject; both events were considered not related to DEX. There were no treatment-emergent SAEs leading to death, no other treatment-emergent SAEs, and no TEAEs that led to DEX discontinuation.

1.2.2. Study DEX-09-08

This study was a Phase II/III, open label, multi-centre, study of the safety, efficacy and PK of dexmedetomidine in neonates aged ⩾ 28 weeks through ⩽ 44 weeks gestational age. The objective was to characterize the safety, efficacy, and pharmacokinetics (PK) of dexmedetomidine administered as an IV loading dose followed by a continuous IV infusion in neonates.

The study design is summarised in Figure 2.

Figure 2



This multicenter study was conducted at 18 sites in the US.

1.2.2.1. Methodology

Study participants

Inclusion criteria

These were as follows: 1) Initially intubated and mechanically ventilated pediatric subjects in an intensive care setting anticipated to require a minimum of 6 hours of continuous IV sedation; 2) The ability to complete all PK sampling and blood draws; 3) Age: subjects had to fit into 1 of the following age ranges at screening: preterm neonates ≥ 28 weeks through < 36 weeks, gestational age; this constituted treatment age group I; term neonates born at ≥ 36 weeks through ≤ 44 weeks gestational age; this constituted treatment age group II (gestation age was calculated as follows: the time elapsed between the first day of the last menstrual period and the day of enrolment), and 4) Weight: subject's weight at the time of enrollment had to be > 1000 g.

Exclusion criteria

These were as follows: 1) Neonate subjects with neurological conditions that prohibited an evaluation of sedation (e.g diminished consciousness from increased intracranial pressure, the presence of catastrophic brain injury or other severe mental disorders that would make responses to sedatives unpredictable and/or measurement of the N-PASS unreliable; subjects with immobility from neuromuscular disease or continuous infusion of NMB agents); 2) Subjects with second degree or third degree heart block unless subject had a pacemaker or pacing wires were in situ; 3) HR < 120 bpm prior to the initiation of DEX.; 4) Exposure to any investigational drug within 30 days prior to DEX administration; 5) Previous exposure to DEX as part of an investigational study; 6) In subjects that were ex-utero for less than 72 hours, a maternal history of poly-substance drug abuse, based upon the investigator's clinical judgment; 7) At the discretion of the investigator, subjects in whom the risk of DEX treatment was expected to exceed its benefits; 8) Subjects who had a known allergy or contraindication to fentanyl, morphine, MDZ, DEX, or other alpha-2 agonists; 9) Requirement for medications other than DEX, MDZ, morphine, or fentanyl for sedation and pain control; 10) Screening ALT levels > 115 U/L.

Treatment

Subjects were sequentially assigned a loading dose (mcg/kg) and continuous infusion dose (mcg/kg/hr) as outlined in Table 3. Subjects were administered a 10 to 20-minute loading dose followed by a maintenance dose of a minimum of 6 hours up to a maximum of 24 hours. At baseline, subjects were assigned into either age group I or age group II based on gestational age; weight criteria were also used to determine PK sampling. Both groups could enrol simultaneously; however, within each group, the next dose level could not begin to enrol until all subjects had completed the previous dose level and the Data Safety Monitoring Board (DSMB) had approved enrolment to the next level.

Table 3 Treatment assignment

Dose Level	Treatment Group: Age Group I ≥ 28 weeks to < 36 weeks gestational age (n)	Treatment Group: Age Group II ≥ 36 weeks to ≤ 44 weeks gestational age (n)	Loading Dose mcg/kg	Continuous Infusion Rate mcg/kg/hr
1	6	8	0.05	0.05
2	6	8	0.1	0.1
3	6	8	0.2	0.2

Rescue medication was administered as needed for sedation (MDZ) and pain (fentanyl or morphine), during DEX administration based on results of the neonatal- Pain, Agitation, Sedation Scale (N-PASS). Rescue therapy was indicated when the total N-PASS score was > 3 or by clinical judgment and whether the subject was intubated or extubated and the selection of sedative rescue or analgesic rescue was at the discretion of the Investigator.

Outcomes/endpoints

Pharmacokinetics

The PK parameters were the same as in study DEX-11-01. Arterial, venous, or capillary blood samples (0.15 mL each) for PK analysis were obtained at 6 or 7 protocol-designated times for subjects in age group I depending upon weight (≥ 28 weeks through < 36 weeks gestational age) and at 7 designated times for subjects in age group II (≥ 36 weeks through ≤ 44 weeks gestational age).

Efficacy

The primary efficacy endpoint for the study was the number of subjects requiring any rescue medication (MDZ) for sedation during DEX infusion.

Secondary efficacy endpoints included: incidence of rescue medication use for analgesia during DEX infusion; (a) The total amount and (b) the weight adjusted total amount (per kg) of rescue medication MDZ, morphine or fentanyl given for sedation and analgesia during DEX infusion; change from baseline in vital signs and oxygenation (SpO2) measures during DEX infusion; time spent with a total N-PASS score > 3 and ≤ 3 during DEX infusion and time to extubation was explored in DEX-exposed subjects.

Statistical methods

The intent-to-treat (ITT) population included all patients who met all of the inclusion criteria, none of the exclusion criteria. The safety evaluable (SE) population included all patients who received DEX. The efficacy evaluable (EE) population was all subjects who received DEX for at least 6 hours. This was the primary population for the efficacy analysis. The PK evaluable population included all patients in the EE population with adequate DEX concentration data. This was the primary population for the PK analysis.The primary analysis, the percentage of subjects that required MDZ for sedation during DEX infusion, was summarised using descriptive statistics. All other endpoints were also summarised using summary statistics. Statistical analyses comparing age groups and dose levels were planned in the protocol for the final analysis, but in the end the study was terminated early before the full amount of patients in age group I were recruited and no formal statistical analysis was conducted.

The sample size was planned based on a pairwise comparison between the high and low dose groups. It was expected that 90% of subjects on the lowest dose would require rescue medication for sedation and 45% in the highest dose group. Thus with 14 patients in each dose group there would be 72% power to detect a difference, assuming a 1-sided test at the 5% level.

1.2.2.2. Results

Recruitment/ Number analysed

Nine sites enrolled 30 subjects for the interim analysis. Data from a further 6 subjects of age group I, dose level 2 were collected after the data cut off of subjects enrolled for the interim analyses and were included in an addendum report.

The study was officially discontinued early on 17 August 2011 for reasons unrelated to safety. A total of 36 subjects have been evaluated out of a total of 42 originally planned. The 6 subjects planned to be enrolled and analyzed for dose level 3 (0.2 mcg/kg loading dose and 0.2 mcg/kg/hr maintenance dosing) for age group I (ages ≥ 28 weeks through < 36 weeks gestational age) were not enrolled or evaluated. See Table 4.

Table 4. Subjects Enrollment

Dose Description				
Level	Dose[a]	Number: Age Group I		Age Group II
1	0.05/0.05	Planned/Actual: Location of Data:	6/6 (Interim)	8/8 (Interim)
2	0.1/0.1	Planned/Actual: Location of Data:	6/6 (Addendum)	8/8 (Interim)
3	0.2/0.2	Planned/Actual: Location of Data:	6/0 (Not Done)	8/8 (Interim)

[a] Entries are Loading Dose (mcg/kg)/Maintenance Dose (mcg/kg/hr)

The data sets analyzed for these interim analyses included EP, EE, ITT, SE, and PK Evaluable Populations as summarized in Table 5 (the EE, ITT, and SE Populations are identical):

Table 5 Number analysed

	Dose Level 1 DEX 0.05[b] (N = 14)	Dose Level 2 DEX 0.1[b] (N = 8)	Dose Level 3 DEX 0.2[b] (N = 8)	Total (N = 30)
EP, EE, ITT, SE Populations (Age Groups I and II)	14 (100.0%)	8 (100.0%)	8 (100.0%)	30 (100.0%)
Age Group I[a]	6 (42.9%)	0	0	6 (20.0%)
Age Group II[a]	8 (57.1%)	8 (100.0%)	8 (100.0%)	24 (80.0%)
PK Evaluable Population (Age Groups I and II)	4 (28.6%)	5 (62.5%)	7 (87.5%)	16 (53.3%)
Age Group I[a]	3 (21.4%)	0	0	3 (10.0%)
Age Group II[a]	1 (7.1%)	5 (62.5%)	7 (87.5%)	13 (43.3%)

[a] Age Group I = ≥ 28 to < 36 weeks gestational age; Age Group II = ≥ 36 to ≤ 44 Weeks.
[b] Units are mcg/kg for loading dose and mcg/kg/hr for maintenance dosing (continuous infusion).
Source: Table 14.1.3

Patient characteristics

The mean gestational age in weeks for age group I was 30.3 weeks; for age group II it was 38.7 weeks. For all 30 subjects in both age groups I and II combined, the mean gestational age in weeks was 37.0 weeks. Predominantly males were enrolled in this study; however, females were predominant in age group I only. The majority of neonates were Caucasian. The mean weight for age group I was 1.38 kg and for age group II, 3.26 kg, and for all 30 subjects in both age groups I and II combined 2.88 kg. A further 6 patients (3 male, 3 female) were recruited after the interim analysis with a mean gestational age of 32.5 weeks. Mean height was 42.75cm and weight 1.71kg. The subjects were all in age group I, dose level 2.

In age group I, cardiopulmonary disease affected 5 subjects (83.3%). Congenital heart disease was present in 1/6 subjects (16.6%). In addition, all subjects in this age group had prematurity-induced respiratory disorders (n=6, 100.0%) and one-half of these had hematologic disease (n=3; 50.0%). No subjects in this age group were post-surgical.

Within age group II, the 3 dose levels had a variety of medical history, more subjects had congenital heart disease and more subjects were post-operative cardiac surgery, particularly in dose level 3. In age group II, congenital heart disease was present in 17/24 subjects (70.8%) as follows: 7 of 8

subjects in dose level 1, 3 of 8 subjects in dose level 2, and 7of 8 subjects in dose level 3. The other most common body systems in this age group were gastrointestinal disease (n=10, 41.7%) and respiratory disease (n=13, 54.2%). Two subjects in dose level 2 had gastroschisis. At the start of study drug administration, 12 of 24 (50.0%) subjects were post-operative surgery: 3 of 8 in dose level 1, 2 of 8 in dose level 2, and 7 of 8 in dose level 3.

Pharmacokinetics

Table. 6 overall results

Pharmacokinetic Parameter (units)	Age Group I[a]	Age Group II[a]		
	Dose Level 1 DEX LD=0.05 mcg/kg MD=0.05 mcg/kg/hr (N=3)	Dose Level 1 DEX LD=0.05 mcg/kg MD=0.05 mcg/kg/hr (N=1)	Dose Level 2 DEX LD=0.1 mcg/kg MD=0.1 mcg/kg/hr (N=5)	Dose Level 3 DEX LD=0.2 mcg/kg MD=0.2 mcg/kg/hr (N=7)
CL (L/hr)	0.49 (n=1)	2.21	1.90 (n=4)	2.33
CL_w (L/hr/kg)	0.41 (n=1)	0.61	0.64 (n=4)	0.73
AUC (0-Last) [(pg/mL)hr]	704.06	431.94	813.26	3694.32
AUC (0-Infinity) [(pg/mL)hr]	853.54 (n=1)	570.66	1478.10 (n=4)	4058.40
$AUC\ (0\text{-}Infinity)_{Dose}$ [(pg/mL)hr/mcg]	2049.32 (n=1)	451.65	524.95 (n=4)	429.33
C_{max} (pg/mL)	101.88	78.45	122.43	325.53
V_d (L)	2.13 (n=1)	10.20	13.10 (n=4)	9.18
V_{dw} (L/kg)	1.79 (n=1)	2.83	4.44 (n=4)	2.87
V_{ss} (L)	3.26 (n=1)	4.90	8.42 (n=4)	6.62
V_{ssw} (L/kg)	2.74 (n=1)	1.36	2.85 (n=4)	2.07
$t_{1/2}$ (hr)	3.02 (n=1)	3.19	4.77 (n=4)	2.73

[a] Age group I = ≥ 28 to < 36 weeks gestational age; Age group II = ≥ 36 to ≤ 44 weeks.
LD=loading dose; MD=maintenance dosing
Source: Tables 14.2.3.1.1 and 14.2.3.2.1

Table. 7 Pharmacokinetic analysis on post-interim patients

Pharmacokinetic Parameter (units)	Age Group I[a] Dose Level 2 DEX Loading Dose=0.1 mcg/kg Maintenance Dosing=0.1 mcg/kg/hr (N=6)
CL (L/hr)	0.48 (n=2)
CL_w (L/hr/kg)	0.29 (n=2)
AUC (0-Last) [(pg/mL)hr]	708.09
AUC (0-Infinity) [(pg/mL)hr]	4305.31 (n=2)
$AUC\ (0\text{-Infinity})_{Dose}$ [(pg/mL)hr/mcg]	2102.55 (n=2)
C_{max} (pg/mL)	107.22
V_d (L)	5.71 (n=2)
V_{dw} (L/kg)	3.47 (n=2)
V_{ss} (L)	6.25 (n=2)
V_{ssw} (L/kg)	3.79 (n=2)
$t_{1/2}$ (hr)	8.32 (n=2)

[a] Age group I = ≥ 28 to < 36 weeks gestational age
Source: Tables 14.2.3.1 and 14.2.3.2

Efficacy

Primary Efficacy

Table 8. Number and percentage of patients requiring any rescue medication for sedation during DEX infusion

Number and Percent of Subjects[a]	Dose Level 1 DEX 0.05[c] N = 14	Dose Level 2 DEX 0.1[c] N = 8	Dose Level 3 DEX 0.2[c] N = 8	Total N = 30
Age Group I[b]	0/6	-	-	0/6
Age Group II[b]	1/8 (12.5%)	1/8 (12.5%)	2/8 (25.0%)	4/24 (16.7%)
Total	1/14 (7.1%)	1/8 (12.5%)	2/8 (25.0%)	4/30 (13.3%)

[a] Number and percent of subjects who received rescue MDZ for sedation during the DEX infusion within each dose level by age group.
[b] Age group I = ≥ 28 to < 36 weeks gestational age; Age group II = ≥ 36 to ≤ 44 weeks.
[c] Units are mcg/kg for loading dose and mcg/kg/hr for maintenance dosing (continuous infusion).
Source: Table 14.2.1.1

Secondary Efficacy

Table 9. Number and Percentage of Subjects Who Received Rescue Medication for Analgesia During DEX Infusion (EE Population)

Number and Percent of Subjects[a]	Dose Level 1 DEX 0.05[c] N = 14	Dose Level 2 DEX 0.1[c] N = 8	Dose Level 3 DEX 0.2[c] N = 8	Total N = 30
Age Group I[b]	1/6 (16.7%)	-	-	1/6 (16.7%)
Age Group II[b]	4/8 (50.0%)	4/8 (50.0%)	6/8 (75.0%)	14/24 (58.3%)
Total	5/14 (35.7%)	4/8 (50.0%)	6/8 (75.0%)	15/30 (50.0%)

[a] Number and percent of subjects who received rescue medication for analgesia during the DEX infusion within each dose level by age group.
[b] Age group I = ≥ 28 to < 36 weeks gestational age; Age group II = ≥ 36 to ≤ 44 weeks.
[c] Units are mcg/kg for loading dose and mcg/kg/hr for maintenance dosing (continuous infusion).
Source: Table 14.2.2.1.1

Table 10. Summary of Subjects Who Received Rescue Medication (EE Population)

Parameter	Age Group I[a]	Age Group II[a]			
	Dose Level 1 DEX 0.05[b] N = 6	Dose Level 1 DEX 0.05[b] N = 8	Dose Level 2 DEX 0.1[b] N = 8	Dose Level 3 DEX 0.2[b] N = 8	Total Age Group II[a] N = 24
Midazolam for Sedation					
n (%)	0	1 (12.5)	1 (12.5)	2 (25.0)	4 (16.7)
Mean total mg ± SD	0	0.36 ± NA	0.50 ± NA	1.13 ± 1.46	0.78 ± 0.94
Mean total mg/kg ± SD Weight Adjusted	0	0.10 ± NA	0.15 ± NA	0.32 ± 0.41	0.22 ± 0.26
Fentanyl for Analgesia					
n (%)	1 (16.7)	4 (50.0)	2 (25.0)	5 (62.5)	11 (45.8)
Mean total mcg ± SD	18.0 ± NA	9.0 ± 6.8	7.5 ± 2.1	9.5 ± 7.5	9.0 ± 6.1
Mean total mcg/kg ± SD Weight Adjusted	16.3 ± NA	2.4 ± 1.6	2.3 ± 0.59	2.7± 2.1	2.5 ± 1.6
Morphine for Analgesia					
n (%)	0	0	2 (25.0)	3 (37.5)	5 (20.8)
Mean total mg ± SD	0	0	0.28 ±0.04	0.40 ± 0.17	0.35 ± 0.14
Mean total mg/kg ± SD Weight Adjusted	0	0	0.13 ±0.03	0.11 ± 0.05	0.12 ± 0.04

[a] Age group I = ≥ 28 to < 36 weeks gestational age; Age group II = ≥ 36 to ≤ 44 weeks.
[b] Units are mcg/kg for loading dose and mcg/kg/hr for maintenance dosing (continuous infusion).
NA=not applicable.
Source: Tables 14.2.2.2.1.1, 14.2.2.2.1.2, 14.2.2.3.1.1.1, 14.2.2.3.1.1.2, 14.2.2.3.2.1.1, 14.2.2.3.2.1.2

Post-interim patients

None of the 6 post-interim analysis patients received rescue MDZ for sedation during the study infusion. 1 subject received rescue medication for analgesia during DEX infusion. This subject received 2 mcg (0.98 mcg/kg) fentanyl for rescue analgesia during DEX infusion.

Safety

Most TEAEs were considered as not related to treatment, 2 subjects in age group II experienced TEAEs considered as related to treatment. There were no severe TEAEs reported, 2 subjects in each age group experienced moderate TEAEs, all other subjects experienced mild TEAEs. There were no treatment-emergent SAEs leading to death, no other treatment-emergent SAEs, and no TEAEs that led to drug discontinuation. There were no dose-limiting toxicities that led to drug discontinuation (persistent bradycardia, persistent hypotension, or respiratory depression). One non-treatment

emergent SAE of cardiac arrest was reported and considered not related to the treatment (pre-existing heart disease).The subject responded to treatment and recovered.

Table 11. Overview of Treatment Emergent Adverse Events

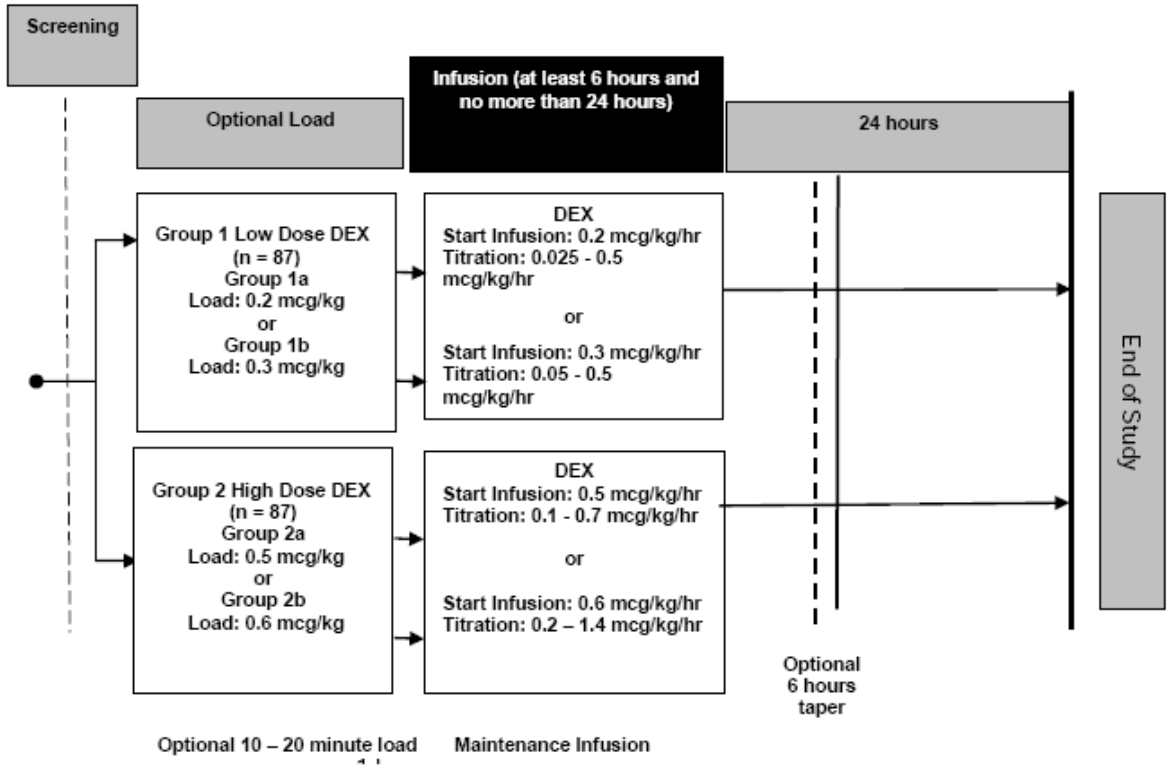
Preferred Term	Age Group I[a]	Age Group II[a]			
	DEX dose Level 1 0.05[b] N = 6	DEX dose Level 1 0.05[b] N = 8	DEX dose Level 2 0.1[b] N = 8	DEX dose Level 3 0.2[b] N = 8	Total Age Group II[a] N = 24
Number of TEAEs	4	7	7	14	28
Subjects with at least 1 TEAE [n (%)]	2 (33.3%)	5 (62.5%)	4 (50.0)%	6 (75.0%)	15 (62.5%)
Blood potassium decreased	0	2 (25.0%)	0	0	2 (8.3%)
Hypokalaemia	0	0	0	3 (37.5%)	3 (12.5%)
Anger	0	0	2 (25.0%)	3 (37.5%)	5 (20.8%)
Atelectasis	0	1 (12.5%)	0	1 (12.5%)	2 (8.3%)
Pleural effusion	0	0	0	2 (25.0%)	2 (8.3%)

[a] Age Group I = ≥ 28 to < 36 weeks gestational age; Age Group II = ≥ 36 to ≤ 44 Weeks.
[b] Units are mcg/kg for loading dose and mcg/kg/hr for maintenance dosing (continuous infusion).
Source: Table 14.3.1.2.2

1.2.3. Study DEX-08-05

This was a phase III, randomized, double-blind, dose-controlled, multicentre study evaluating the safety and efficacy of dexmedetomidine in intubated and mechanically ventilated paediatric ICU patients. The objectives were: 1) to characterize the loading and maintenance dosing of DEX by age group and overall medical condition of pediatric subjects; 2) to evaluate the safety and efficacy of loading and maintenance infusions for sedation in initially intubated and mechanically ventilated paediatric ICU subjects; and 3) to explore the exposure-response relationship between dose of DEX and clinical measures of sedation and safety. The study design is summarised in Figure 3.

Figure 3



Subjects were randomized into 1 of 2 treatment groups: high dose DEX and low dose DEX. There was no placebo arm. Within each treatment group, the loading and maintenance doses were stratified according to the presence or absence of cardiopulmonary bypass (CPB): 1) Group 1 = low dose DEX; 2) Group 2 = high dose DEX; 3) Group 1a and 2a = post CPB (DEX started within 24 hours after end of surgery) ; 4) Group 1b and 2b = all other diagnoses. Subjects were also grouped by age; age group 1 included subjects ⩾1 month to <24 months old (if premature, corrected for gestational age until 3 months of actual birth age); age group II included subjects ⩾24 month to <17 years old.

1.2.3.1. Methodology

Study participants

Inclusion criteria

These were as follows: 1) Initially intubated and mechanically ventilated pediatric subjects (⩾1 month (birth age corrected for prematurity) to <17 years of age) in an intensive care setting. The means by which the subject was intubated could include nasotracheal, endotracheal or via tracheotomy. The subject must have been mechanically ventilated prior to and during the commencement of study drug; 2) Anticipated to require a minimum of 6 hours of continuous intravenous (IV) sedation; 3) American Association of Anesthesiologists (ASA) physical status classification: P1, P2, P3, or P4; 4) A UMSS score of 1, 2, 3, or 4 at the start of infusion of study drug and 5) A dose had been established for this subject's age.

Exclusion criteria

These were as follows: 1) Subjects with neurological conditions that prohibited an evaluation of sedation in the opinion of the investigator (e.g., increased intracranial pressure or extensive brain

surgery); 2)The infusion pump minimal capacity could not accommodate the lowest possible maintenance infusion rate of study drug based on subject's weight; 3) Subjects with second degree or third degree heart block unless subject had a pacemaker or pacing wires; 4) Hypotension that persisted beyond a 15-minute period of re-assessment prior to starting study drug: age 1 month to ⩽6 months old: SBP <60 mmHg, age >6 months to <2 years old: SBP <70 mmHg, age >2 to <12 years old: SBP <80 mmHg and age >12 to <17 years old: SBP <90 mmHg; 5) Pre-existing bradycardia that persisted beyond a 15-minute period of re-assessment prior to starting study drug: age 1 month to <2 months old: HR <90 bpm, age ⩾2 months to <12 months old: HR <80 bpm, age ⩾12 months to <2 years old: HR <70 bpm, age ⩾2 to <12 years old: HR <60 bpm, age ⩾12 to <17 yrs old: HR <50 bpm; 6) ALT/ SGPT: 1 month to 12 months old: >165 U/L, >12 months to <17 years old: ⩾100U/L; 7) Subjects had a known allergy to DEX, MDZ, morphine, or fentanyl; 8) Requirement for medications other than DEX, MDZ, morphine, or fentanyl for sedation and pain control and 9) Subjects with immobility from neuromuscular disease, paralysis from administration of NMB agents, spinal cord injury above T5 or subjects with muscle weakness from congenital or systemic medical illness etiologies, subjects who received NMB agents intraoperatively had to be, in the investigator's opinion, free of residual neuromuscular blockade prior to dosing with study drug.

Treatment

Treatment could be administered as follows: 1) an optional 10-20 minute loading dose infusion of DEX followed by a continuous titratable maintenance dose infusion of DEX for a minimum of 6 hours up to 24 hours. It was recommended that subjects who were on open-label DEX prior to starting the study not receive a loading dose, but the decision was at the discretion of the Investigator; or 2) No loading dose and a continuous titratable maintenance dose infusion of DEX for a minimum of 6 hours up to 24 hours. It was to be administered through a designated IV line or port on a central line. The doses were according to Table 12:

Table 12- Doses administered

AGE ≥1 month - <17 years (If premature corrected for gestational age until 3 months of actual birth age)			
		Treatment Groups	
	Diagnosis	Group 1 Low dose	Group 2 High dose
a	s/p CPB	Loading dose: 0.2 mcg/kg Maintenance dose titration range (0.025 – 0.5 mcg/kg/hr)	Loading dose 0.5 mcg/kg Maintenance dose titration range (0.1 – 0.7 mcg/kg/hr)
b	All other diagnoses	Loading dose 0.3 mcg/kg Maintenance dose titration range (0.05 – 0.5 mcg/kg/hr)	Loading dose 0.6 mcg/kg Maintenance dose titration range (0.2 – 1.4 mcg/kg/hr)

The target UMSS was a score between 1-3. If required, MDZ could be titrated as a rescue medication at the discretion of the investigator as follows: <6 months: 0.05-0.1 mg/kg; 6 months to 5 years old : 0.05-0.1 mg/kg; 6 to 12 years old: 0.025-0.05 mg/kg; >12 (Adult): 1-3 mg.

If rescue MDZ was considered necessary, the DEX dose was titrated upwards and the need to administer additional midazolam reassessed following DEX administration. Fentanyl or morphine could be administered to treat pain, after the subject was first treated with an increase in the DEX infusion rate, at age-specific doses, or as a continuous infusion at the discretion of the investigator. Subjects

receiving continuous infusions of fentanyl or morphine prior to randomization could continue these infusions throughout study drug administration if required.

Outcomes / endpoints

The primary efficacy endpoint was the percent of subjects that did not require rescue midazolam for sedation based on achieving and maintaining a target UMSS score of 1-3 while intubated.

Secondary endpoints included the absolute time and percentage of time on study drug that the subject was in a UMSS score range of 1 to 3 while intubated; absolute time and percentage of time on study drug that the subject was out of the target sedation range while intubated (UMSS score of 0 or 4); total amount of rescue medication required for sedation and analgesia; time to first dose of rescue medication for sedation and analgesia; and time to extubation.

Statistical Methods

The study was powered to give 80% power at the 2-sided 5% level to detect a difference of 17-20% in the proportion of patients not requiring rescue MDZ. The rate on the high dose group was assumed to be around 62-77%. Three analysis populations were defined. The intent-to-treat (ITT) population included all randomised subjects; the safety evaluable (SE) population included all patients that received any dose of Dexdor; the efficacy evaluable (EE) population included all patients who received Dexdor for at least 6 hours. The EE population was primary for the analysis of efficacy. The primary efficacy variable, the percentage of patients that did not require rescue MDZ (based on achieving and maintaining a target UMSS range of 1-3 while intubated), was compared between treatment groups using the normal approximation to the binomial distribution. The absolute time and the percentage time on study drug that the patient was in a UMSS range of 1-3 while intubated were compared between treatment groups using a Wilcoxon test. Time to successful extubation, and time to first dose of rescue medication for sedation and analgesia while on study drug were compared between treatment groups using a log-rank test and summarised using Kaplan-Meier estimates.

1.2.3.2. Results

Recruitment / Number analysed

Table 13. Number of patients in each group

	Group 1 Low Dose			Group 2 High Dose		
	s/p CPB[a] N = 36	Other Dx[b] N = 53	Total N = 89	s/p CPB[c] N = 37	Other Dx[d] N = 49	Total N = 86
Age Group I[e]	25	38	63	26	34	60
Age Group II[f]	11	15	26	11	15	26
Total	36	53	89	37	49	86

Dx = diagnosis
[a] Dex dose is loading dose (LD) = 0.2/Maintenance dose (MD) = 0.025 – 0.5 mcg/kg/hour
[b] Dex dose is LD = 0.3/MD = 0.05 – 0.5 mcg/kg/hour
[c] Dex dose is LD = 0.5/MD = 0.1 – 0.7 mcg/kg/hour
[d] Dex dose is LD = 0.6/MD = 0.2 – 1.4 mcg/kg/hour
[e] Age group I = ≥1 month to <24 months;
[f] Age group II = ≥24 months to <17 years old

Table 14.

Number of patients in the analysis populations

Population	Low dose	High dose
ITT	89	86
SE	89	86
EE	83 (93.3%)	81 (94.2%)

Time to extubation was analyzed for measurable assessment and 41 subjects were excluded from this analysis.

Patient characteristics

In age group I, median age was 8.51 months (low dose) and 9.75 months (high dose); in age group II, median age was 6.32 years (low dose) and 7.57 years (high dose). Subjects had similar screening ASA classification in both age groups and both DEX dose groups with the majority of subjects high risk with severe systemic disease, P3. Subjects who underwent open-heart surgery (s/p CPB) were mostly high risk P3 and there were similar numbers of subjects in the low dose (72.2%) and high dose (73.0%) DEX groups s/p CPB.

Median age of subjects was similar across dose groups and by underlying condition; median age of age groups combined was 10.7 months (range: 0.9 months to 16.3 years) in the low dose group and 14.7 months (range: 1.3 months to 16.2 years) in the high dose group. Height and weight were similar across dose groups and by underlying condition (median height of age groups combined: low dose 68.0 cm, high dose 76.5 cm; median weight of age groups combined: low dose 8.1 kg; high dose 8.5 kg).

Overall, approximately 70.0% of subjects were Caucasian (low dose, 71.9%; high dose, 72.1%). Slightly more subjects overall were male than female (low dose, 59.6% male; high dose, 55.8% male). Most subjects had cardiopulmonary disease at baseline. Body systems in which 50.0% or more subjects overall had at least 1 report were cardiopulmonary (low dose, 73.0%; high dose, 81.4%) and respiratory (low dose, 55.1%; high dose, 61.6%).

All subjects (100.0%) in the high dose group and all except 1 subject in the low dose group received at least 1 concomitant medication during the study. Concomitant medications taken by at least 50.0% of subjects in a dose group, excluding MDZ, fentanyl, and morphine, the use of which was permitted as rescue medication per protocol, were furosemide, acetaminophen, potassium chloride, and heparin. In the s/p CPB groups following open heart surgery, >90% of subjects were on inotropic support postop. Inotropic support with milrinone and dobutamine was similar in both the low and high dose DEX groups s/p CPB.

The most common reason for study discontinuation was loss to follow-up: 6 (6.7%) subjects in the low dose group and 7 (8.1%) in the high dose group did not complete the post-dose day 28 follow-up. Other reasons for study discontinuation were AE and physician reason: 2 (2.2%) subjects in the low dose group and 1 (1.2%) in the high dose group. Other discontinuations included death unrelated to DEX (1 (1.2%) subject each in the low dose and high dose groups), and discontinuation due to data that were not collected.

Efficacy

Primary Efficacy

Table 15 . Percentages of subjects that did not require rescue MDZ for sedation while intubated during the treatment period

Number and Percent of Subjects[a]	Group 1 Low Dose s/p CPB DEX dose	Group 1 Low Dose Other Dx DEX dose	Group 1 Low Dose Total	Group 2 High Dose s/p CPB DEX dose	Group 2 High Dose Other Dx DEX dose	Group 2 High Dose Total
Total ASA Class	N = 33	N = 50	N = 83	N = 34	N = 47	N = 81
Age Group I[b]	5 (15.2)	20 (40.0)	25 (30.1)	10 (29.4)	20 (42.6)	30 (37.0)
Age Group II[c]	4 (12.1)	8 (16.0)	12 (14.5)	7 (20.6)	7 (14.9)	14 (17.3)
Total	9 (27.3)	28 (56.0)	37 (44.6)	17 (50.0)	27 (57.4)	44 (54.3)
ASA Class: P1, P2	N = 8	N = 21	N = 29	N = 5	N = 16	N = 21
Age Group I[b]	1 (12.5)	8 (38.1)	9 (31.0)	1 (20.0)	7 (43.8)	8 (38.1)
Age Group II[c]	0	4 (19.0)	4 (13.8)	0	2 (12.5)	2 (9.5)
Total	1 (12.5)	12 (57.1)	13 (44.8)	1 (20.0)	9 (56.3)	10 (47.6)
ASA Class: P3, P4	N = 25	N = 29	N = 54	N = 29	N = 31	N = 60
Age Group I[b]	4 (16.0)	12 (41.4)	16 (29.6)	9 (31.0)	13 (41.9)	22 (36.7)
Age Group II[c]	4 (16.0)	4 (13.8)	8 (14.8)	7 (24.1)	5 (16.1)	12 (20.0)
Total	8 (32.0)	16 (55.2)	24 (44.4)	16 (55.2)	18 (58.1)	34 (56.7)

[a] Number and percent of subjects who did not require rescue MDZ for sedation based on achieving and maintaining a target UMSS range of 1 to 3 while intubated.
[b] Age group I = ≥1 month to <24 months
[c] Age group II = ≥24 months to <17 years old

Table 16. statistical results

Underlying Condition/ Age Group	Group 1 Low Dose	Group 2 High Dose	Difference (Group 1 – 2)[b]	p-value[c]
Total ASA Class				
All Diagnoses [n (%)][a]	37/83 (44.6)	44/81 (54.3)	-9.74	0.2751
Age Group I[d]	25/57 (43.9)	30/56 (53.6)	-9.71	0.3984
…Age Group II[e]	12/26 (46.2)	14/25 (56.0)	-9.85	0.6723
s/p CPB [n (%)]	9/33 (27.3)	17/34 (50.0)	-22.73	0.0974
Age Group I[d]	5/22 (22.7)	10/23 (43.5)	-20.75	0.2461
Age Group II[e]	4/11 (36.4)	7/11 (63.6)	-27.27	0.3938
Other Diagnoses [n (%)]	28/50 (56.0%)	27/47 (57.4%)	-1.45	1.0000
Age Group I[d]	20/35 (57.1)	20/33 (60.6)	-3.46	0.9653
…Age Group II[e]	8/15 (53.3)	7/14 (50.0)	3.33	1.0000
ASA Class: P1, P2				
All Diagnoses [n (%)][a]	13/29 (44.8)	10/21 (47.6)	-2.79	1.0000
Age Group I[d]	9/19 (47.4)	8/15 (53.3)	-5.96	1.0000
Age Group II[e]	4/10 (40.0)	2/6 (33.3)	6.67	1.0000
s/p CPB [n (%)]	1/8 (12.5)	1/5 (20.0)	-7.50	1.0000
Age Group I[d]	1/6 (16.7)	1/3 (33.3)	-16.67	1.0000
Age Group II[e]	0/2	0/2	0.00	--
Other Diagnoses [n (%)]	12/21 (57.1)	9/16 (56.3)	0.89	1.0000
Age Group I[d]	8/13 (61.5)	7/12 (58.3)	3.21	1.0000
…Age Group II[e]	4/8 (50.0)	2/4 (50.0)	0.00	1.0000
ASA Class: P3, P4				
All Diagnoses [n (%)][a]	24/54 (44.4)	34/60 (56.7)	-12.22	0.2645
Age Group I[d]	16/38 (42.1)	22/41 (53.7)	-11.55	0.4228
…Age Group II[e]	8/16 (50.0)	12/19 (63.2)	-13.16	0.6594
s/p CPB [n (%)]	8/25 (32.0)	16/29 (55.2)	-23.17	0.1515
Age Group I[d]	4/16 (25.0)	9/20 (45.0)	-20.00	0.3722
Age Group II[e]	4/9 (44.4)	7/9 (77.8)	-33.33	0.3336
Other Diagnoses [n (%)]	16/29 (55.2)	18/31 (58.1)	-2.89	1.0000
Age Group I[d]	12/22 (54.5)	13/21 (61.9)	-7.36	0.8573
…Age Group II[e]	4/7 (57.1)	5/10 (50.0)	7.14	1.0000

[a] Subjects who did not require rescue MDZ for sedation based on achieving and maintaining a target UMSS range 1-3 while intubated.
[b] Mean difference between treatment groups in percentage of subjects who did not require rescue MDZ for sedation based on achieving and maintaining a target UMSS of 1-3 while intubated.
[c] P-value for risk difference for 2x2 table from Chi-Square test with continuity correction.
[d] Age group I = ≥1 month to <24 months
[e] Age group II = ≥24 months to <17 years old

Secondary Efficacy

There was no significant difference between treatment groups for the absolute time and percentage of time that subjects were in the UMSS range 1-3 during the treatment. All age groups and diagnoses receiving the high dose of DEX were in the targeted UMSS range 87.8 to 99.2% of the time compared to 85.5 to 99.0% of the time in the low dose DEX groups.

Differences between treatment groups in total amount of rescue medication required for sedation (MDZ) or analgesia (fentanyl and morphine) are presented in Tables 17-19.

Table 17.

Differences Between Treatment Groups in Total Amount of Rescue Medication (MDZ) Required for Sedation during Treatment Period While Intubated
Efficacy Evaluable Population

Underlying conditions /group subject[e]	Group 1 Low Dose n/N Mean(mg)	Group 2 High Dose n/N Mean(mg)	Difference (mg) (Group 1 - Group 2)[a]	P-Value[d]
Rescued Subjects[b]				
All Diagnoses	46/83 (4.01)	37/81 (2.72)	1.29	0.6868
Age Group I	32/57 (2.93)	26/56 (2.52)	0.41	0.7663
Age Group II	14/26 (6.47)	11/25 (3.18)	3.29	0.8908
s/p CPB	24/33 (2.11)	17/34 (2.16)	-0.06	0.4584
Age Group I	17/22 (1.95)	13/23 (2.22)	-0.27	0.5717
Age Group II	7/11 (2.49)	4/11 (1.99)	0.50	0.5690
Other Diagnoses	22/50 (6.08)	20/47 (3.19)	2.90	0.1737
Age Group I	15/35 (4.04)	13/33 (2.82)	1.22	0.3447
Age Group II	7/15 (10.46)	7/14 (3.86)	6.60	0.2764
All Subjects[c]				
All Diagnoses	83/83 (2.22)	81/81 (1.24)	0.98	0.1914
Age Group I	57/57 (1.64)	56/56 (1.17)	0.47	0.2867
Age Group II	26/26 (3.48)	25/25 (1.40)	2.09	0.4851
s/p CPB	33/33 (1.53)	34/34 (1.08)	0.45	0.2029
Age Group I	22/22 (1.51)	23/23 (1.25)	0.25	0.3730
Age Group II	11/11 (1.58)	11/11 (0.72)	0.86	0.3801
Other Diagnoses	50/50 (2.68)	47/47 (1.36)	1.32	0.5682
Age Group I	35/35 (1.73)	33/33 (1.11)	0.62	0.5729
Age Group II	15/15 (4.88)	14/14 (1.93)	2.95	0.8141

[a] Mean differences between treatment groups in total amount of rescue medications required for sedation and analgesia during treatment period while intubated.
[b] Subjects who were required rescued medication (MDZ).
[c] Subjects who did not receive rescue medication whose dose was calculated as zero.
[d] Wilcoxon test
[e] Age Group I: >= 1 month to < 24 months; Age Group II: >=24 months to < 17 yrs old

Table 18

Differences Between Treatment Groups in Amount (Per Kg Basis) of Rescue Medication (Fentanyl) Required for Analgesia during Treatment Period While Intubated
Efficacy Evaluable Population

Underlying conditions /group subject[e]	Group 1 Low Dose n/N Mean(mcg/kg)	Group 2 High Dose n/N Mean(mcg/kg)	Difference(mcg/kg) (Group 1 - Group 2)[a]	P-Value[d]
Rescued Subjects[b]				
All Diagnoses	53/83 (8.06)	44/81 (5.89)	2.18	0.5355
Age Group I	34/57 (10.68)	32/56 (6.49)	4.19	0.1563
Age Group II	19/26 (3.37)	12/25 (4.28)	-0.91	0.8552
s/p CPB	24/33 (4.93)	17/34 (4.78)	0.15	0.9894
Age Group I	16/22 (6.05)	13/23 (5.40)	0.65	0.8780
Age Group II	8/11 (2.69)	4/11 (2.76)	-0.07	0.9823
Other Diagnoses	29/50 (10.65)	27/47 (6.58)	4.07	0.4217
Age Group I	18/35 (14.80)	19/33 (7.23)	7.57	0.0917
Age Group II	11/15 (3.86)	8/14 (5.03)	-1.18	0.7726
All Subjects[c]				
All Diagnoses	83/83 (1.99)	81/81 (1.13)	0.86	0.2916
Age Group I	57/57 (2.30)	56/56 (1.32)	0.98	0.4562
Age Group II	26/26 (1.32)	25/25 (0.72)	0.60	0.2679
s/p CPB	33/33 (1.83)	34/34 (1.34)	0.50	0.3134
Age Group I	22/22 (2.36)	23/23 (1.68)	0.67	0.5228
Age Group II	11/11 (0.78)	11/11 (0.60)	0.17	0.3174
Other Diagnoses	50/50 (2.10)	47/47 (0.99)	1.11	0.6282
Age Group I	35/35 (2.26)	33/33 (1.06)	1.20	0.6798
Age Group II	15/15 (1.72)	14/14 (0.81)	0.90	0.6084

Note: Screening Weight is used when Baseline Weight is not available for CPB subjects and Screening Weight is used for all other subjects.
[a] Mean differences between treatment groups in total amount of rescue medications required for sedation and analgesia during treatment period while intubated.
[b] Subjects who were required rescued medication (Fentanyl).
[c] Subjects who did not receive rescue medication whose dose was calculated as zero.
[d] Wilcoxon test
[e] Age Group I: >= 1 month to < 24 months; Age Group II: >=24 months to < 17 yrs old

Table 19.

Age Group I: >= 1 month to < 24 months[a]

	Group 1 Low Dose			Group 2 High Dose		
Total Amount of Morphine	s/p CPB Dex Dose	All other diagnoses Dex Dose	Total	s/p CPB Dex Dose	All other diagnoses Dex Dose	Total
(mg/kg)	(N = 22)	(N = 35)	(N = 57)	(N = 23)	(N = 33)	(N = 56)
Rescued Subjects[b]						
N	15 (68.2%)	9 (25.7%)	24 (42.1%)	14 (60.9%)	7 (21.2%)	21 (37.5%)
Mean	0.246	0.813	0.459	0.203	0.316	0.241
SD	0.1717	1.3211	0.8389	0.1289	0.2002	0.1606
Min	0.07	0.11	0.07	0.05	0.09	0.05
Q1	0.096	0.118	0.107	0.138	0.096	0.138
Median	0.203	0.314	0.231	0.155	0.346	0.167
Q3	0.414	0.400	0.407	0.263	0.556	0.350
Max	0.61	4.10	4.10	0.50	0.57	0.57
All Subjects[c]						
N	22 (100.0%)	35 (100.0%)	57 (100.0%)	23 (100.0%)	33 (100.0%)	56 (100.0%)
Mean	0.065	0.145	0.114	0.040	0.030	0.034
SD	0.0520	0.6825	0.5342	0.0429	0.0686	0.0591
Min	0.00	0.00	0.00	0.00	0.00	0.00
Q1	0.000	0.000	0.000	0.000	0.000	0.000
Median	0.075	0.000	0.000	0.049	0.000	0.000
Q3	0.102	0.047	0.096	0.053	0.000	0.052
Max	0.17	4.05	4.05	0.15	0.27	0.27

Note: Screening Weight is used when Baseline Weight is not available for CPB subjects and Screening Weight is used for all other subjects.
[a] By age group I, II and combine.
[b] Number of subjects who received any amount (>0) of rescue medication for analgesia during the treatment period while intubated; and % of those within each treatment group. Descriptive statistics below for total amount of Morphine are computed based on number of subjects that used any amount (>0) of rescue medication for analgesia during the treatment period while intubated within each treatment group.
[c] Subjects who did not receive rescue medication whose dose was calculated as zero.

Safety

TEAEs were experienced by 33/63 subjects (52.4%; 82 events) in the low dose group and 27/60 subjects (45.0%; 57 events) in the high dose DEX group. In age group II, TEAEs were experienced by 15/26 subjects (57.7%; 39 events) in the low dose group and 16/26 subjects (61.5%; 31 events) in the high dose DEX group. In age group I, moderate and severe TEAEs were experienced by 17 (27.0%; 30 events) and 10 subjects (16.7%; 17 events) in the low and high dose groups, respectively; and in age group II, moderate and severe TEAEs were experienced by 8 (30.8%; 13 events) and 6 subjects (23.1%; 9 events) in the low and high dose groups, respectively.

Overall, 5/175 subjects (2.9%) reported a total of 7 severe TEAEs; all severe TEAEs were reported in the low dose DEX groups. The severe TEAEs reported were myocarditis, pyrexia, status epilepticus, dyspnea, ventricular fibrillation, chest pain, and wheezing. The severe myocarditis event was also considered a serious TEAE and treatment-related. There were 4 deaths and these were considered not related to DEX.

Treatment-emergent mild blood cortisol increased was experienced by 1 subject (1.7%) in the age group I, in high dose DEX and other diagnoses group, and was considered not related to DEX. All subjects studied had an increase in cortisol in response to cosyntropin (ACTH) 1 hour after discontinuing DEX. There was no evidence of adrenal suppression based on cortisol levels at the time of discontinuation of DEX or with the cortisol response to cosyntropin.

1.2.4. Additional analysis

A population PK (PPK) analysis was performed by the MAH with the following objectives : 1) to conduct an exploratory review of data from four studies in paediatric patients in order to characterise the data and evaluate the assumptions and appropriateness of the model to be developed; 2) to develop a PPK model describing the PK of Dexdor in paediatric subjects (including neonates); and 3) assess the influence of demographic covariates and concomitant medications on the variability in the PPK model parameters.

A total of 184, 427, 615, and 54 dexmedetomidine concentration records from 30, 35, 54, and 5 pediatric subjects enrolled in studies DEX-09-08, DEX-08-05 (CHOP), DEX-08-01 and DEX-11-01, respectively, were included. Of the 124 subjects, a sizable number were below the age of two (n=62, 50%) with 28 pre-term and term neonates (22% of total), 14 between the ages of 1 and 6 months (11%), 15 between 6 months and 1 year (12%) and 13 between 12 months and 2 years (11%).

The applicant conclusions were as follows:

- The final base structural PK model was a 2-compartment model with interindividual variability (IIV) estimated on clearance (CL), intercompartmental clearance (Q), volume of the central compartmental (Vc), and volume of the peripheral compartment (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:

Model based on post-natal age and categorical indicator for pre-term and term neonates
$\text{Typical}\,\text{CL} = 10.7 \cdot \left(\frac{\text{WTKG}}{9.6}\right)^{[0.75\cdot(1+0.53)\cdot NEO]}$
$\text{Typical}\,\text{V}_\text{c} = 8.49 \cdot \left(\frac{\text{WTKG}}{9.6}\right)$
$\text{Typical}\,\text{Q} = 63.5 \cdot \left(\frac{\text{WTKG}}{9.6}\right)^{0.75} \cdot \left(\frac{age}{1.31}\right)^{-0.342}$
$\text{Typical}\,\text{V}_\text{p} = 14.7 \cdot \left(\frac{\text{WTKG}}{9.6}\right) \cdot \left(\frac{age}{1.31}\right)^{-0.280}$

WTKTG: weight in kg, NEO: indicator variable for neonates

- The intercompartmental clearance and the volume of the peripheral compartment for dexmedetomidine 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 dexmedetomidine pharmacokinetic 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.
- Using the final population PK model for dexmedetomidine, 95% confidence intervals expressed relative to the corresponding point estimates of the geometric mean of the CL and Vc were within the targeted range of 0.6 to 1.4, except in the 6-17 years age group where the upper bound on Vc was 1.43, however all confidence interval bounds were well within the range when PK parameters were adjusted for body weight.

Additional analysis using model based on PMA

At the CHMP request, the applicant provided additional analyses of maturation using different ages (PNA: postnatal age, PMA: post-menstrual age: post, GA: gestational age). The resulting model based on PMA showed a very different structural model equation from the original PNA model:

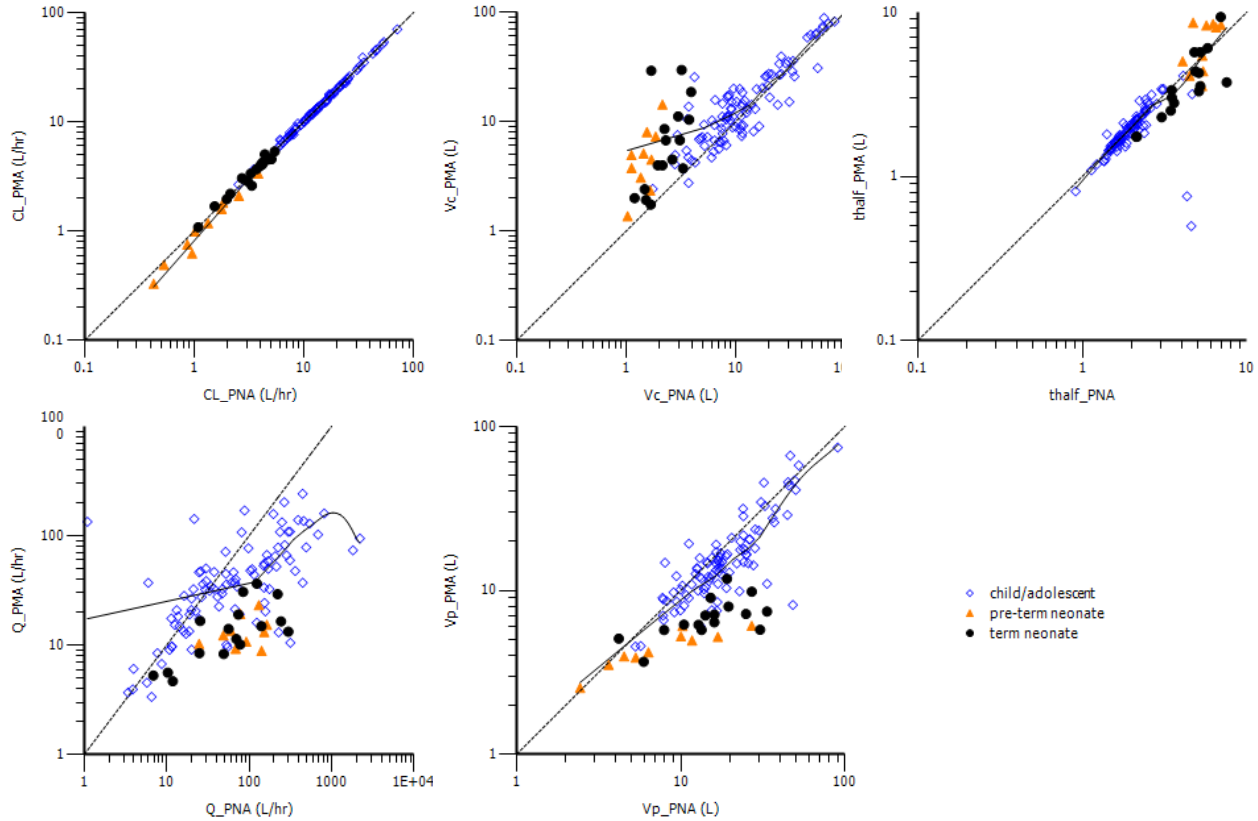
Model based on post-menstrual age
$\text{Typical CL} = 11.4 \cdot \left(\frac{\text{WTKG}}{10.35}\right)^{0.75} \cdot \left(\frac{PMA^{7.41}}{0.676^{7.41} + PMA^{7.41}}\right)$
$\text{Typical V}_c = 13.4 \cdot \left(\frac{\text{WTKG}}{10.35}\right) \cdot \left(\frac{PMA}{2.06}\right)^{-0.379}$
$\text{Typical Q} = 36.5 \cdot \left(\frac{\text{WTKG}}{10.35}\right)^{0.75}$
$\text{Typical V}_p = 13.9 \cdot \left(\frac{\text{WTKG}}{10.35}\right) - 1.74 \cdot (PMA - 2.06)$

According to the applicant, despite this finding, the PK of dexmedetomidine in the pediatric population was statistically significantly related to both body weight and maturation in both models.

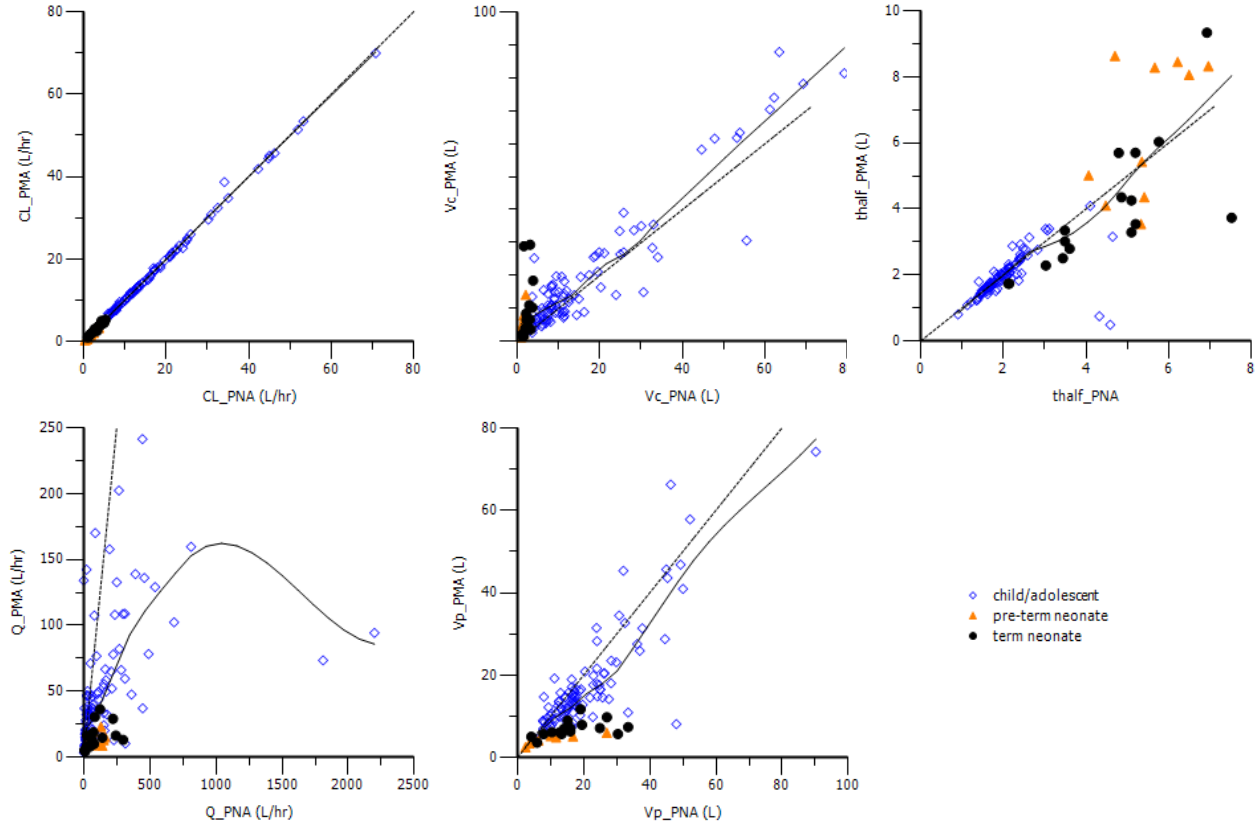
Comparison of individual Bayesian estimates of pharmacokinetic parameters using models based on PNA and PMA – CHMP analysis

This comparison is presented in Figures 5-15.

Figures 5-10 Comparison of individual bayesian estimates of pharmacokinetic parameters derived from the original model based on post-natal age (PNA) and the current model based on post-menstrual age (PMA) shown on log-log axes.



Figures 11-15 Comparison of individual bayesian estimates of pharmacokinetic parameters derived from the original model based on post-natal age (PNA) and the current model based on post-menstrual age (PMA) shown on linear axes.



In these figures, pre-term and term neonates are differentiated by symbol. A dashed line indicates a 1:1 relationship (i.e. identical estimates from the two models) and a solid line indicates LOESS regression line. Linear scale (data source: Appendix 12 of Population PK report of June 6, 2012 and Appendix 19 of Response Memorandum of October 22, 2012; thalf calculated CHMP).

1.2.5. Discussion

Across the completed paediatric studies, Dexdor has been studied in neonates, infants, children and adolescents aged from gestational age 28 weeks to 17 years. The doses studied have ranged from 0.05 - 7 µg/kg/hr given for a maximum of 24 hours.

Study DEX-11-01 (12 months to <24 months)

According to the applicant, exposure to DEX, measured as Cmax or AUC, appeared to be dose-related, although highly variable. Mean Cmax increased from 4500 pg/mL in dose level 1 to 11737 pg/mL in dose level 2, while dose adjusted Cmax was fairly constant. Likewise, AUC (0-Infinity) increased from 4639 (pg/mL)hr in dose level 1 to 14204 (pg/mL)hr in dose level 2, whereas dose-adjusted AUC (0-Infinity) was fairly constant. Dexmedetomidine half-life was about 2 hours in all subjects and was independent of dose. With the exception of one outlier in dose level 1, both CL and CLw were fairly constant across both dose levels. Clearance was about 5.7 L/hr (2.5 to 8.2 L/hr) whereas weight adjusted CL was about 0.6 L/hr/kg (0.2 to 0.9 L/hr/kg). Vd was also fairly constant across both dose levels. Again with the exclusion of the outlier in dose level 1, Vd was about 16.2 L (13.4 to 19.9 L) whereas weight adjusted Vd was about 1.6 L/kg (0.99 to 2.23 L/kg).

The CHMP was of the opinion that given the small number of patients included (n=5), labelling an individual as an 'outlier' could be questioned and therefore from the CHMP viewpoint, the results in this study may only conclude to a very high inter-individual variability with regard to pharmacokinetics. It is known from the adult patient population PK that dexmedetomidine appeared to exhibit an essentially linear relationship at steady state between infusion rate and plasma concentration and the plasma clearance of dexmedetomidine is approximately constant within the anticipated therapeutic infusion dose range. The mean estimate of the elimination t1/2 is approximately 1.9 to 2.5 hours (min 1.35 h and max 3.68 h). On this basis, no major findings are identified in this study performed in a small patient population and the PK profile appeared to be behave similarly to that in the adult population. No conclusions could be drawn regarding pharmacokinetic-pharmacodynamic profile and efficacy, due to the small number of patients.

Study DEX-09-08 (>28 weeks to <44 weeks gestational age)

In this study, the ITT, SE and EE populations were identical. Although, no statistical analysis was performed due to early termination of the study, the sample size calculation could be questioned as 1-sided tests at the 5% level are not usually accepted. The CHMP noted that study DEX-09-08 seeks to further characterise the PK and efficacy of Dexmedetomidine in neonates, one of the paediatric population where these data were currently lacking.

No subject in age group I received rescue MDZ for sedation during the study infusion. In age group II, a total of 4 subjects (16.7%) received rescue MDZ for sedation during the study infusion: 1 subject each (12.5%) in dose level 1 and dose level 2, and 2 subjects (25.0%) in dose level 3, resulting in a combined age group I and II total of 4 subjects (13.3%). None of the 6 post-interim analysis patients

received rescue MDZ for sedation during the study infusion. 1 subject received rescue medication for analgesia during DEX infusion. This subject received 2 mcg (0.98 mcg/kg) fentanyl for rescue analgesia during DEX infusion. One subject (16.7%) in age group I received rescue medication for analgesia during the study infusion. In age group II, a total of 14 subjects (58.3%) received rescue medication for analgesia during the study infusion: 4 subjects each (50.0%) in dose level 1 and dose level 2, and 6 subjects (75.0%) in dose level 3, resulting in a combined age group I and II total of 15 subjects (50.0%).

More subjects in age group II were post-operative surgical, particularly dose level 3 where most subjects were post-operative open heart surgery for congenital heart disease and likely required more medication for sedation and analgesia. In addition, the 8 subjects in age group II, dose level 3 received maintenance dosing for a median duration of nearly 3 times longer than subjects in dose levels 2 and 1. The premature neonates in age group I were adequately sedated with DEX alone and only 1 subject required additional rescue for pain. The low doses of DEX, up to 0.2 mcg/kg/hr, used in this trial in the term neonates was not sufficient to consistently sedate and keep this age group comfortable. It is noted that in dose level 3 includes more post-surgical patients which may have influenced the increased analgesic requirements.

Despite the small numbers of patients; the clearance of Dexdor appeared to be lower in the younger children (Cl:0.49, Clw:0.41 in Age group I, 28-36 weeks). This finding is consistent with the work of Potts AL et al. who found that children younger than one year of age might have lower bodyweight-adjusted clearances when compared to older children and adults implying that higher steady-state dexmedetomidine plasma concentrations would be predicted when dosing in proportion to bodyweight.

The predicted higher exposures were borne out in study DEX-09-08. This finding may have contributed to the lower requirement for rescue medication in the younger patient age group, although no clear dose response relationship could be elucidated. No discussion is provided as to the correlation between N-PASS scores and UMSS scores, although the CHMP accepted that both are validated scales for their respective age groups.

In this study, Dexdor appeared to exhibit a level of efficacy similar to that seen in older children and adults and is reasonably well tolerated.

Study DEX-08-05 (≥1 month to <17 years)

In this study, the definition of the EE population could be questioned as all patients randomised and treated should have been included in the efficacy analysis (ie patient who failed to receive 6 hours treatment with Dexdor were excluded, however such failure could be related to the performance of the product for that patient). Considering that the number of patients excluded from the EE population was small and fairly balanced across the treatment groups, the CHMP was of the opinion that this exclusion criteria did not hamper the validity of the presented results.

The study showed that Dexdor was able to maintain paediatric patients across different age groups and ASA status' at a target level of sedation in approximately 50% of cases. From the data of the initial MAA, this figure is slightly less than the proportion of adult subjects who were maintained at target sedation levels of approximately 60%. Overall, the results are difficult to interpret since the study failed to show a statistically significant difference between the doses (as was planned for in the sample size calculation). Comparing the observed results with the estimates used for the study planning it is clear that this is because the high dose was worse than expected. Nevertheless, no significant difference between the dose groups was observed in terms of the primary or secondary endpoints, nor

was any subgroup difference identified. In the absence of a placebo arm (or an even lower dose) it cannot be determined whether the study had sufficient assay sensitivity to detect an important difference between the doses should one exist. A further possibility is that the studied doses were 'too high' and on the flatter part of the dose-response curve – and there was truly no important difference between the doses. The CHMP was however reassured that no significant observations were made with regard to safety. It is noted that that a greater proportion of TEAEs were observed in the lower dose group than the high dose group.

Overall the high dose DEX group was numerically better sedated than the low dose DEX groups with 54.3% of high dose subjects not requiring rescue MDZ compared to 44.6% in the low dose DEX groups. A smaller percentage of subjects in age group II did not require rescue MDZ for sedation in comparison with age group I in both DEX dose groups. In both dose groups subjects undergoing open heart surgery with CPB received more rescue MDZ than those in the other diagnoses groups. The greatest difference between treatment groups was in the heart surgery subjects (s/p CPB) with more subjects in both age groups receiving high dose DEX than low dose DEX, not requiring MDZ sedation rescue. The pattern of results was similar whether subjects were more (ASA Classification P3, P4) or less critically ill (ASA Classification P1, P2).

There was no significant difference between treatment groups for the absolute time and percentage of time that subjects were in the UMSS range 1-3 during the treatment. All age groups and diagnoses receiving the high dose of DEX were in the targeted UMSS range 87.8 to 99.2% of the time compared to 85.5 to 99.0% of the time in the low dose DEX groups.

No difference was observed between groups for the amount of rescue midazolam, or requirement for rescue fentanyl or morphine for analgesia.

Population pharmacokinetic analysis

Of the 124 subjects included in the analysis, a sizable number were below the age of two (n=62, 50%) with 28 pre-term and term neonates (22% of total), 14 between the ages of 1 and 6 months (11%), 15 between 6 months and 1 year (12%) and 13 between 12 months and 2 years (11%). The CHMP agreed that the ages and weights represented in the 4 studies comprise a continuum of maturation and size (pre-term and term neonates to nearly adults) and that the younger age range, where maturation is expected to play an important role, is well represented within the data set.

The methodology utilised for model development and evaluation is clearly described and is generally supported. One of the studies included in the present population PK analysis (CHOP) was previously analysed and reported (Su 2010) and appeared to have been used as a starting point for the present analysis. However, the description of Su's structural model was inconsistent in the presented analysis and hence the CHMP could not endorse the applicant conclusions. On this basis and considering the different maturation status expected in preterm versus term neonates, age effects on Q and Vp and that the presented data was only based on post-natal age, additional analysis where CL and Q are related to $WT^{0.75}$ and Vc and Vp are related to WT^{1} as a base model and exploratory plots of CL ($L/h/kg^{0.75}$) and Vc, Q and Vp versus age (PNA, PMA, GA) were provided. The resulting model based on PMA showed very different structure for inclusion of maturation effects on the pharmacokinetic parameters for dexmedetomidine compared to the original model utilising post-natal age. A comparison of the empirical bayes estimates derived from the two models based on log-log and linear scales was made, showing that despite the different approach to inclusion of age in the two models, the resulting empirical bayes estimates of clearance were very similar with only very small differences for pre-term neonates. This was however not true for any of the other model parameters, where the values differed (often markedly) between the two models (see Figure 5-15). Despite these differences,

the two models predicted similar concentration-time profiles for individual subjects and also show similar visual predictive checks.

Overall, the CHMP concluded that the relationship of drug clearance to age and weight was viewed as well estimated. Also, the terminal half-life (thalf) is judged to be generally very similar between the two models. When the mean values of CL and half-life for each age group are compared between the two models, they are in all cases less than 15% different from one another. Thus, both models were judged to provide useful and reliable estimates of these parameters and inclusion of such information in section 5.2 of the SmPC was endorsed by the CHMP.

1.3. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (new text= underlined, deleted text: strikethrough):

Summary of Product Characteristics

Section 4.2

Paediatric population: ~~The safety and efficacy of Dexdor in children aged 0 to 18 years has not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made~~. A dosing scheme similar to adults has been used in a predominantly post-operative ICU population aged >1 month, during use for up to 24 hours. A loading dose of around 0.5 to 1 mcg/kg over 10 to 20 minutes was commonly used in the studies but is probably not needed if the patient is already established on sedation. Treatment for longer than 24 hours has not been studied. In new-born infants maintenance doses above 0.2 mcg/kg/h have not been evaluated.

Section 4.8

Paediatric population

~~There is limited experience in children, most data has been obtained from short term exposure.~~ Children > 1 month post-natal, predominently post-operative, have been evaluated for treatment up to 24 hours in the ICU and demonstated a similar safety profile as in adults. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to maintenence doses ≤ 0.2 mcg/kg/h. A single case of hypothermic bradycardia in a neonate has been reported in the literature.

Section 5.1

~~Paediatric efficacy data from well controlled ICU studies is sparse but dexmedetomidine has been used as a sedative in children~~Evidence of paediatric efficacy was seen in a dose-controlled ICU study in a largely post-operative population aged 1 month to ≤ 17 years. Most patients were successfully sedated with dexmedetomidine during treatment up to 24 hours, although a difference between dose levels of dexmedetomidine was not demonstrated. Data on treatment for > 24 hours is not available. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to low doses (≤ 0.2 mcg/kg/h) (see sections 5.2 and 4.4). New-born infants may be particularly sensitive to the bradycardic effects of Dexdor in the presence of hypothermia and in conditions of heart rate-dependent cardiac output.

Section 5.2

~~Data in children 2 months to 17 years of age are limited. Dexmedetomidine half-life appears similar to that seen in adults. In the age groups 2-20 months and 2-6 years, body weight-adjusted plasma clearance appeared higher (1.2 and 1.0 l/h/kg, respectively) but decreased in older children (0.8 l/h/kg) to be comparable to adults (0.5-0.6 l/h/kg). Plasma clearance may be lower in children~~

~~< 2 months due to immaturity.~~Data in new-born infants (28 – 44 weeks gestation) to children 17 years of age are limited. Dexmedetomidine half life in children (2 months to 17 years) appears similar to that seen in adults but in new-born infants (28 – 44 weeks gestation) it appears higher. In the age groups 2-20 months and 2-6 years, body weight-adjusted plasma clearance appeared higher (1.2 and 1.0 l/h/kg, respectively) but decreased in older children (0.8 l/h/kg) to be comparable to adults (0.5-0.6 l/h/kg). Body weight-adjusted plasma clearance in new-born infants (28 weeks gestation to 1 month) appeared lower (0.9 l/h/kg) than in the age groups 2-20 months due to immaturity.

During the procedure, the CHMP requested further amendments to the PI including the deletion of the dosing information in section 4.2 since the present application was not related to a paediatric indication and the inclusion in section 5.2 of a table with both mean values of the clearance and half life and some estimates of variability. The CHMP considered the MAH proposal to state that "the clearance in older children decreased to be comparable to clearance in adults (0.5 - 0.6 L/h/kg)" was misleading. The point estimate of clearance for the 6 - 17 year olds was 0.8 and confidence interval 0.69 to 0.92 L/h/kg. The requested amendments in addition to revision of part of the proposed text in section 5.1 were agreed by the MAH. The final recommended PI changes by the CHMP can be read as follows:

Section 4.2

*Paediatric population***:** Currently available data are described in sections 4.8, 5.1, 5.2 but no recommendation on a posology can be made.

Section 4.8

Paediatric population

Children > 1 month post-natal, predominently post-operative, have been evaluated for treatment up to 24 hours in the ICU and demonstrated a similar safety profile as in adults. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to maintenance doses ≤ 0.2 mcg/kg/h. A single case of hypothermic bradycardia in a neonate has been reported in the literature.

Section 5.1

Evidence of paediatric efficacy was seen in a dose-controlled ICU study in a largely post-operative population aged 1 month to ≤ 17 years. Approximately 50% of patients treated with dexmedetomidine did not require rescue addition of midazolam during a median treatment period of 20.3 hours, not exceeding 24 hours. Data on treatment for > 24 hours is not available. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to low doses (≤ 0.2 mcg/kg/h) (see sections 5.2 and 4.4). New-born infants may be particularly sensitive to the bradycardic effects of Dexdor in the presence of hypothermia and in conditions of heart rate-dependent cardiac output.

Section 5.2

Data in new-born infants (28 - 44 weeks gestation) to children 17 years of age are limited. Dexmedetomidine half life in children (1 months to 17 years) appears similar to that seen in adults, but in new-born infants (under 1 month) it appears higher. In the age groups 1 months to 6 years, body weight-adjusted plasma clearance appeared higher but decreased in older children. Body weight-adjusted plasma clearance in new-born infants (under 1 month) appeared lower (0.9 l/h/kg) than in the older groups due to immaturity. The available data is summarised in the following table:

		Mean (95% CI)	
Age	N	Cl (l/h/kg)	t1/2 (h)
Under 1 month	28	0.93 (0.76, 1.14)	4.47 (3.81, 5.25)
1 to < 6 months	14	1.21 (0.99, 1.48)	2.05 (1.59, 2.65)
6 to < 12 months	15	1.11 (0.94, 1.31)	2.01 (1.81, 2.22)
12 to < 24 months	13	1.06 (0.87, 1.29)	1.97 (1.62, 2.39)
2 to < 6 years	26	1.11 (1.00, 1.23)	1.75 (1.57, 1.96)
6 to < 17 years	28	0.80 (0.69, 0.92)	2.03 (1.78, 2.31)

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Italy. Annex II was also updated in accordance with the latest template.

2. Overall conclusion and impact on the benefit/risk balance

On the basis of the submitted data, the CHMP concluded that the update of the Product Information to include new paediatric information from new-born infants (28 - 44 weeks gestation) to adolescents aged 17 years old, was adequate. The CHMP considered that this change does not affect the benefit risk profile of the product which remains positive.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC to revise the paediatric information based on the results of new paediatric studies submitted in accordance with article 46 of the Paediatric Regulation. Details of the local representative in Italy were updated. Linguistic changes are made in the following countries: Greece, France, Italy, Czech Republic. Annex II was also updated in accordance with the latest template.