# CLINICAL REVIEW

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|---|---|
| Application Type | NDA |
| Application Numbers | 021038 S012 & 022 |
| Priority or Standard | Priority |
| Submit Date | 14 Dec 2012 |
| Received Dates | 17 & 18 Dec 2012 |
| PDUFA Goal Date | 17 Jun 2013 |
| Division / Office | ODE II / DAAAP |
| Reviewer Name | Leah Crisafi, MD |
| Review Completion Date | 23 May 2013 |
| Established Name | Dexmedetomidine HCl |
| Trade Name | Precedex® |
| Therapeutic Class | Alpha$_2$-adrenoreceptor agonist |
| Applicant | Hospira, Inc. |
| Formulation | Intravenous |
| Dosing Regimen | (b) (4) |
| Indication | Sedation of intubated, mechanically ventilated ICU patients |
| Intended Population | (b) (4) |

Template Version: March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

(b) (4)

:

(1) The use and accounting of all medications and particularly rescue medications does not allow for interpretation of the safety and efficacy data.
(2) The studies did not demonstrate substantial evidence of effectiveness, having failed at their primary endpoints.
(3) Safety assessment is not possible because identification of adverse events lacked objectivity and consistency, and reported adverse events lacked detail necessary for understanding and verifying severity of recorded hemodynamic adverse events.
(4) A possible safety signal for hypotension is present.
(5) The data is not generalizable.
(6) The submission provided difficulty in review, due to inconsistent variables and definitions across datasets for the different studies, and due to limited data regarding the administration of concomitant medications.

## 1.2 Risk Benefit Assessment

This risk benefit discussion is focused of the risks and benefits of labeling the drug with safety information only, because the drug was not shown to be efficacious in the submitted studies.

Issue 1 – Use of Other Medications

In this submission, the Applicant carefully accounted for only the administration of midazolam (MDZ), and planned to analyze only midazolam's use as rescue. The Applicant thereby underestimated the incidence of rescue administration, leaving the reviewer without details required to understand the extent and contribution of other types of rescue, nor information about other types of medications that are important for assessing the study drug's safety profile.

Details regarding timing and dosing of medications were not recorded by the Applicant. With the exception of midazolam, those medications that were ordered on an as needed basis were given at unknown times and often in unknown total quantities. Also, many medications were administered as infusions, and may have been titrated up to deepen

sedation that was attributed by the Applicant to the study drug. However, only in the case of midazolam was information about those changes provided.

For example, the Applicant does not currently have and did not provide details regarding the dosing of fentanyl and/or morphine for the 58% of subjects who received those medications during dexmedetomidine (DEX) for indications other than pain. The Applicant also does not have details regarding medications administrated to the 24.5% of subjects who required other forms of sedation rescue, such as chloral hydrate and lorazepam.

Another factor confounding the interpretation of the use of rescue is the Applicant's determination that a medication would only be considered as rescue if the medication was started after initiation of DEX. Therefore, orders for sedating medications like lorazepam and diazepam for treatment of "irritability" may have been administered to subjects during DEX treatment and not considered as rescue because they were ordered prior to DEX initiation. Moreover, those 33.2 percent of subjects who were counted as not requiring rescue may have, in fact, received rescue medications that were ordered on a scheduled, as needed, or infusion basis, but the Applicant does not have the data regarding when such medications were actually administered. Therefore, one doesn't know what contribution those medications made to the subjects' depth of sedation.

Also problematic is the analysis of safety using this database, for two reasons. First, without being able to quantify and evaluate concomitant medications, one cannot conclude that the safety profile observed in the trials reasonably represents the safety of the study drug. In addition, the absence of detailed information about administration other drugs, particularly those used in the setting of hemodynamic events or lability, leaves the reviewer unable to independently judge the severity of adverse events and draw conclusions about the study drug's safety.

Issue 2 – Failure of Primary Endpoints

In essence, the Application consisted of two efficacy trials, and both failed to demonstrate their primary endpoint. DEX-08-05 was a dose-controlled, assessor-blinded trial and represented the older pediatric subjects; its failed primary endpoint was a difference in the percentage of subjects not receiving rescue midazolam. DEX 09-08 was a dose-controlled open-label study in the youngest group of subjects; its failed primary endpoint was a difference in the incidence of midazolam rescue.

Labeling the study drug with safety information for pediatric use when the doses studied were ineffective might lead to underestimation of the study drug's risks. In particular, safety labeling might encourage use of the study drug at higher doses than were

evaluated in this submission, because sedation drugs are often titrated to effect and many subjects were not adequately sedated by the doses that were studied.

Issue 3 – Adverse Event Reporting

Two fundamental issues decrease the reliability of the adverse events that the sponsor reported. First, hemodynamic adverse events were not defined in the protocols, despite DEX's known hemodynamic side effects in adults. Second, during adverse events, there was no consistent recording of vital signs.

Hemodynamic adverse events were not standardized across protocols because they were not defined *priori*, leading to uncertainty about the adverse event incidence reported by the Applicant. The lack of standard adverse event definitions led to a remarkable difference in the incidence of adverse events across studies. For example, there was a large difference in the rate of hemodynamic adverse events CHOP study versus the trials that were conducted by the Applicant, where hypertension qualifying as an adverse event was at each investigator's discretion. For example, twelve percent of all subjects were enrolled in the CHOP study, but 79 percent of the 84 cases of treatment-emergent hypertension occurred at CHOP. Eight percent of the non-CHOP subjects who were, like CHOP subjects, aged 1 month to < 2 years and underwent cardiopulmonary bypass (CPB), had a treatment-emergent adverse event of hypertension versus 66 percent of CHOP subjects.

Hemodynamic events with clinical significance were not consistently reported as adverse events, because the presence of an adverse event and its severity was at the discretion of each investigator. And because vital signs were not recorded during adverse events, the reviewer can make no judgment as to whether adverse events were classified correctly. In addition, the narrative summaries often do not fill in these important details. For example, the submission does not include a single blood pressure reading during a 100 minute adverse event of hypotension, during which study drug was interrupted, in a subject who ultimately died.

Issue 4 – Hypotension Signal

As described in above in Issue 3 – Adverse Event Reporting, there were concerning cases of hypotension that were not consistently considered adverse events or were missing important details for understanding severity. Two of the deaths may have been precipitated by hypotension, but the cases lack sufficient detail to make that determination. In addition, there are numerous cases of subjects experiencing significant hypotension without an associated adverse event, and these subjects often had incomplete vital sign documentation.

Issue 5 – Generalizability

The generalizability of efficacy and safety data is questionable, because 50 percent of subjects had undergone cardiopulmonary bypass, and according to the Applicant, cardiopulmonary bypass alters pharmacokinetics. In DEX-08-05, the only clinical trial where the reason for intubation was specified, few subjects were intubated for reasons other than cardiac surgery (48 percent) or respiratory disease (34 percent). Therefore, DEX-08-05, like the submission as a whole, reflects a disproportionately large percentage of cardiac patients and a disproportionately small percentage of subjects intubated for other reasons.

Another problem with generalizability is the striking predominance of subjects who underwent cardiopulmonary bypass in the pharmacokinetic subpopulation. All pharmacokinetic data for subjects aged one to twelve months were from CHOP, and all subjects in the CHOP study underwent cardiopulmonary bypass. Therefore, all subjects aged one month to one year with pharmacokinetic data underwent cardiopulmonary bypass. Among subjects with pharmacokinetic data that were greater than one year of age, 76 percent had undergone cardiopulmonary bypass. The pharmacokinetic results in this submission should not be generalized to the entire pediatric population without first comparing the pharmacokinetic data from subjects who underwent cardiopulmonary bypass with the limited number of subjects who did not.

# 2 Introduction and Regulatory Background

The Sponsor's objective for this submission was to:

- Secure pediatric exclusivity

(b) (4)

## 2.1 Product Information

Dexmedetomidine (DEX; Precedex®) is a selective $\alpha_2$-agonist. It is indicated for the sedation of intubated and mechanically ventilated patients during treatment in an intensive care setting for infusions of no more than 24 hours, and for procedural sedation.

## 2.2 Tables of Currently Available Treatments (b) (4)

(b) (4)

**Table 1 Currently Approved Drugs for Pediatric ICU Sedation**

| Drug | Population |
|---|---|
| Midazolam | Intubated pediatric patients including neonates |

## 2.3 Availability of Proposed Active Ingredient in the United States

DEX was approved in the United States on December 17, 1999.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The labeling for Precedex contains the following WARNINGS AND PRECAUTIONS:

- **Hypotension, bradycardia and sinus arrest:**
  - Have occurred in young healthy volunteers with high vagal tone or with different routes of administration, e.g., rapid intravenous or bolus administration.
  - DEX may exacerbate bradycardia induced by vagal stimuli
  - May be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in the elderly.
  - Use with caution in patients with advanced heart block or severe ventricular dysfunction.
  - Caution with concomitant vasodilators or negative chronotropic agents, although an additive pharmacodynamic effect was not observed in clinical trials.
- **Transient hypertension:** During loading due to initial peripheral vasoconstriction; reduction of the loading infusion rate may be desirable.
- **Arousability:** Patients may appear arousable and alert when stimulated; this alone should not be considered as lack of efficacy.
- **Withdrawal:** With administration up to seven days, subjects may experience withdrawal symptoms, most commonly nausea, vomiting, and agitation. Tachycardia and hypertension requiring supportive therapy may occur.
- **Tolerance and tachyphylaxis:** With exposure beyond 24 hours, and an associated dose-related increase in adverse reactions.
- **Hepatic impairment:** Dose-reduction may be appropriate as clearance decreases with severity of hepatic impairment.

- **Co-administration with other vasodilators or negative chronotropic agents:** Use with caution (b) (4)

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Detailed descriptions of the regulatory activity regarding this Written Request are available in the primary reviews of Medical Officers Schultheis and Simone. This section provides a summary of regulatory activity.

Prior to Written Request

12/17/99
NDA 021038 approval: DEX HCL was initially approved for sedation of intubated and mechanically ventilated patients during treatment in an intensive care setting for ≤ 24 hours. This submission fulfills a Written Request originally issued by the FDA on 3/14/2007 for the study of dexmedetomidine in initially intubated and mechanically ventilated pediatric subjects in the intensive care setting.

2/24/06
Hospira requested that the FDA issue a Written Request.

6/27/07
FDA declined to issue a Written Request in a letter: *We reviewed your proposed pediatric study request and are unable to issue a Written Request based on your submission*.

10/6/06
Hospira and FDA met to discuss a Written Request.

10/31/06
Hospira requested that FDA issue a Written Request.

Written Request Issuance

3/14/07
FDA issued a Written Request.

After Written Request Issuance

10/10/07
A Type B meeting took place.

5/7/10
Hospira requested that FDA amend the Written Request.

12/14/10
Amendment #1 to FDA's Written Request was granted, with changes to *II. Efficacy and safety studies and to the timeframe for report submission.*

5/7/10
Hospira requested that FDA amend the Written Request Amendment #1.

8/30/11
Amendment #2 to FDA's Written Request was granted, with changes throughout.

11/3/11
A Type A meeting took place, where the Sponsor requested further amendment to the Written Request, which was not granted, and further clarification of the Written Request was provided.

Final Pediatric Written Request[1]

- PHARMACOKINETIC STUDIES

*Type of studies:*

These studies will be of open-label, dose-escalation design to obtain pharmacokinetic, pharmacodynamic (PD), safety, and efficacy information in order to identify PK variation among different age groups for comparison with the adult PK profile, and to identify the appropriate dosage to be used for different age groups in the subsequent studies. Information will be collected to evaluate the pharmacokinetics of a loading dose infusion and maintenance dose infusion of dexmedetomidine studied by age cohort beginning with pediatric patients who are at the least risk as defined by the inclusion and exclusion criteria. In order to obtain adequate data for PK/PD analyses, a minimum of three escalating loading doses will be evaluated for each age group. Patients who appear to respond favorably from administration of the loading dose will continue to receive dexmedetomidine by a continuous infusion. The rationale for the choice of doses will be

1 Copied directly from PWR Amendment #2 August 30, 2011

provided in the submitted protocols. This rationale may be informed by literature, or current medical practice, and/or dosing in adults.

*Objective of studies:*

- Characterize the pharmacokinetic profile of dexmedetomidine infusion following a loading dose and maintenance infusion in different pediatric age groups.
- Obtain adequate pediatric PK data to allow for comparison with adult PK data.
- Identify appropriate dosage(s) to be used for different age groups in the subsequent studies, based on comparative exposures related to those in adults or pharmacokinetic/pharmacodynamic analyses.

*Number of patients and age groups in which studies must be performed:*

Studies must include an adequate number of patients to characterize the key pharmacokinetic parameters of dexmedetomidine and to inform the selection of a therapeutic dose for the age ranges studied, taking into account inter-subject variability. The number of patients must be approximately evenly distributed between genders and must be approximately evenly distributed across the age ranges studied. The number of patients required by age group should be adequate to precisely estimate the PK parameters and must be distributed approximately equally among the doses evaluated. The pediatric PK studies need to be adequately powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for a drug in each age group to be studied. These groups have been determined by assessment of differences in developmental physiology.

- > 28 weeks gestational age to <1 month chronological age
- 1 month to < 6 months
- 6 months to < 12 months
- 12 months to < 24 months
- 2 years to < 6 years
- 6 years to < 16 years

A sufficient number of blood samples should be drawn during and after the loading infusion and maintenance infusion to capture the dexmedetomidine PK profile. The total volume of blood drawn and the PK methods to be employed in the data analysis should be determined *a priori* and stated in the protocol. If sparse sampling methods, i.e., population pharmacokinetics, are employed, blood samples should be dispersed throughout the loading infusion, maintenance infusion, and end of infusion periods to ensure proper parameter estimation.

**Inclusion criteria:**

- Initially intubated and mechanically ventilated pediatric subjects in an intensive care setting

**Exclusion criteria:**

- Pediatric patients with neurological conditions that prohibit an evaluation of sedation, such as diminished consciousness from increased intracranial pressure or extensive brain injury. Patients with immobility from neuromuscular disease or neuromuscular blocking agents will be excluded from these studies.

- Patients in whom the risk of dexmedetomidine treatment is expected to exceed its benefits, such as patients with second- or third-degree heart block or protocol-defined significant hepatic impairment.

*Study Endpoints:*

1. Pharmacokinetics:

Descriptive statistics must be reported employing traditional or population PK methods for PK parameters of dexmedetomidine, such as Tmax, t1/2, Cmax, AUC0-t, AUC0-inf, Ke (elimination rate constant), Vd (volume of distribution), and CL (clearance).

Pharmacodynamic and safety measures described below must be measured at the same time points as PK sampling, to the extent possible, to provide an understanding of the concentration-response relationship. Exposure (infusion rate/dose/AUC/Cmax) must be explored with regard to:

- pharmacodynamic endpoints, such as sedation, time to use of rescue medication, amount of rescue sedation

- safety endpoints, such as heart rate, systolic and diastolic blood pressure and most frequent adverse events

2. Pharmacodynamics:

Age-appropriate sedation scale(s) must be used. The rationale for the choice of the scale(s) and instruments must be provided in the protocol. The same age-appropriate instruments must be used at each study site. Sedation is to be measured at the same time points as PK sampling to provide an understanding of the concentration-response relationship.

All protocols must describe the ascertainment of any painful interventions that may affect study assessments. Protocols must specify the recording and evaluation of the extent to which comfort measures are employed and the patients' responses to handling or other stimuli. Additionally, all protocols must specify that the instruments chosen to evaluate sedation in pediatric patient population subsets will be uniform among study centers.

3. Safety:

- Vital signs (heart rate, blood presssure, respiratory rate, pulse oximetry and/or noninvasive carbon dioxide monitoring, EKG, central body temperature, body weight, input/output fluid balance)

- Incidence of adverse events. Measurements of vital signs and laboratory values that exceed prespecified age-appropriate boundaries will be reported as adverse events

- Preterm infants will be assessed for the occurrence of comorbidities of prematurity, such as intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and persistent ductus arteriosus

- Use of rescue regimens to support vital signs

- Use of adjunct medications

- Incidence of signs of withdrawal including changes in blood pressure

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board with prespecified study stopping rules must be stipulated by study protocols.

II. EFFICACY AND SAFETY STUDIES

These studies will be randomized, assessor-blinded, dose-controlled, multicenter trials based upon the dose-ranging findings of the initial pharmacokinetic studies. A separate open-label study will be conducted for the 28 weeks gestational age to <1 month chronological age group. Efficacy will be evaluated based on the percentage of patients who do not require rescue midazolam sedation using a validated, age-appropriate clinical sedation scale. The study population will require sedation for mechanical ventilation for less than 24 hours. The overall study population must encompass a broad range of underlying surgical and medical conditions that require sedation for mechanical ventilation. The protocol must include dosing guidelines that are appropriate to the patient's underlying condition as well as their age. For example, sedation dosing requirements in patients recovering from burn injury are likely to be higher than in

patients following intracranial or heart surgery. Further PK data may be collected in the efficacy and safety studies to broaden an understanding of the pharmacokinetic variables and the understanding between pharmacokinetic variables and safety and efficacy endpoints.

*Objectives of Studies:*

- Characterize the loading and maintenance dosing of dexmedetomidine by age group and overall medical condition of patients.

- Evaluate the safety and efficacy of loading and maintenance infusion for sedation in intubated and mechanically ventilated pediatric patients.

- Explore the exposure-response relationship between any available plasma concentrations of dexmedetomidine and age-appropriate validated clinical measures of sedation and safety.

*Number of Patients and Age Groups in which studies must be performed:*

These groups have been determined by assessment of differences in developmental physiology.

- ≥ 28 weeks gestational age to <1 month chronological age
- 1 month to < 6 months
- 6 months to < 12 months
- 12 months to < 24 months
- 2 years to < 6 years
- 6 years to ≤ 16 years

A sufficient number of patients to provide a power of at least 80% to detect a statistically significant difference in the primary efficacy endpoint must complete the studies. Pediatric patients must be approximately evenly distributed between genders and must be approximately equally distributed across the specified age groups and within the age groups. A sufficient number of pediatric patients must complete the studies to adequately characterize common adverse events with the study drug at clinically relevant doses.

**Inclusion criteria:**

- Initially intubated and mechanically ventilated pediatric subjects in an intensive care setting

- Patients classified as American Society of Anesthesiology (ASA) 1 - 4 for presurgical morbidity

**Exclusion criteria:**

- Pediatric patients with neurological conditions that prohibit an evaluation of sedation, such as diminished consciousness from increased intracranial pressure or extensive brain injury. Patients with immobility from neuromuscular disease or neuromuscular blocking agents will also be excluded from these studies

- Patients in whom the risk of dexmedetomidine treatment is expected to exceed its benefits such as second- or third-degree heart block or protocol-defined significant hepatic impairment

*Study Endpoints:*

1. Efficacy:

   Validated, age-appropriate sedation scale(s) must be used. The same scales must be used across all study sites. The rationale for the choice of the scale(s) and instruments must be provided in the protocol.

   The primary efficacy analysis will be the percentage of subjects who do not require rescue midazolam for sedation based on achieving and/or maintaining the protocol-specified sedation range using validated and age-appropriate sedation scale(s) when intubated. Criteria for administration of concomitant drugs that can result in sedation must be prespecified and the time of administration of these drugs relative to sedation assessments must be captured. All evaluations will be based upon assessments by blinded assessors.

   Secondary endpoints must include the absolute time and the percentage of time of dexmedetomidine treatment that the patient is sedated within a prespecified range, the amount of rescue medication required, and the time to extubation. The time to first use of rescue sedation and/or analgesic medication must also be analyzed.

   All protocols must describe the ascertainment of any painful interventions that may affect study assessments. Protocols must specify recording and evaluation of the extent to which comfort measures are employed and the patients' responses to handling or other stimuli. Additionally, all protocols must specify that the instruments chosen to evaluate sedation in pediatric patient population subsets will be uniform among study centers.

2. Safety:

   - Vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and/or noninvasive carbon dioxide monitoring, EKG, central body temperature, body weight, input/output fluid balance
   - Incidence of adverse events. Measurements of vital signs and laboratory values that exceed prespecified, age-appropriate boundaries will be reported as adverse events
   - Preterm infants will be assessed for the occurrence of comorbidities of prematurity such as intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and persistent ductus arteriosus
   - Use of medications to support vital signs
   - Use of adjunct medications
   - Incidence of signs of withdrawal including changes in blood pressure

   All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board with prespecified study stopping rules must be stipulated by study protocols.

3. Pharmacokinetics:

If additional PK assessments (traditional or population PK) are made, descriptive statistics should be reported for PK parameters of dexmedetomidine, such as Tmax, t1/2, Cmax, AUC0-t, AUC0-inf, Ke (elimination rate constant), Vd (volume of distribution), and CL (clearance).

*Pediatric patients ≥ 28 weeks gestational age to < l month chronological age:*
An open-label study will be conducted for pediatric patients ranging in age from ≥ 28 weeks gestational age to < 1 month chronological age. The study population will require sedation for mechanical ventilation for less than 24 hours. This study will utilize the same inclusion and exclusion criteria and study endpoints described above for older patients; however, it will not be powered based on the primary efficacy endpoint. A minimum of 30 fully evaluable subjects need to complete the study. These subjects should be distributed across the age group and include at least 18 subjects < 36 weeks gestational age and a minimum of 24 subjects ≥ 36 weeks gestational age. For each age subgroup, a minimum of three dexmedetomidine infusion rates need to be evaluated including 0.05, 0.1, and 0.2 mcg/kg/h. For each of the infusion rates required to be studied, a minimum of 6 subjects < 36 weeks gestational age and a minimum of 8

subjects ≥ 36 weeks gestational age need to be fully evaluated for safety and efficacy. A descriptive analysis of safety and efficacy assessment similar to those conducted for pediatric patients ranging from 1 month to ≤ 16 years of age are to be reported.

**Drug Information***:*

*Dosage form:* Approved intravenous formulation, 118 mcg of dexmedetomidine HCl (equivalent to 100 mcg dexmedetomidine base) and 9 mg of sodium chloride in 1 mL water. The solution is preservative-free and contains no additives or chemical stabilizers

*Route of administration:* Iintravenous infusion

*Regimen:* Initial dosing in the pharmacokinetics trials will be selected based on adult dosing requirements, literature, current medical practice, data that the company owns, and/or data to which the company has right of reference. Initial dosing in the efficacy trials will be informed by the PK studies. Subsequent dosing in all trials will be given according to criteria established in the protocol. The dose characteristics (dose in mcg/kg, duration of bolus period where applicable) must be pre-specified in the protocol and recorded in the CRF.

*Drug-specific safety concerns:*

Adverse event monitoring must include, at a minimum, the following:

- Respiratory depression
- Bradycardia
- Hypotension
- Signs of withdrawal after discontinuation of dexmedetomidine, such as rebound hypertension
- Clinical and laboratory signs and/or symptoms of adrenal suppression including hypotension and/or electrolyte abnormalities
- Appropriate clinical laboratory assessments

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board with pre-specified study stopping rules shall be included in all studies.

*Statistical information:*

The pharmacokinetic and pharmacodynamics studies will provide key dosing information for the efficacy trials and the studies should be powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for a drug in each age group to be studied.

Efficacy trials must be powered using information from the pharmacokinetic studies and references. The sample size for the treatment arms will be determined based on the estimates of the effect size for the primary efficacy endpoint to show treatment differences. A detailed statistical analysis plan is required prior to beginning enrollment and should accompany the study protocol submission.

A sufficient number of pediatric patients of both genders should complete the studies to adequately characterize the safety of the study drug at clinically relevant doses. Demographic and safety data should be tabulated and a descriptive analysis of safety data should be provided.

*Representation of Ethnic and Racial Minorities:*

The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

*Extraordinary results:*

In the course of conducting this study, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a similar sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

*Labeling that may result from the studies:*

Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies.

*Format of reports to be submitted:*

You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino. Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/cder/guidance/6766fnl.pdf.

*Timeframe for submitting reports of the studies:*

Reports of the above studies must be submitted to the Agency on or before April 15, 2013. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

*Response to Written Request:*

As per the Best Pharmaceuticals for Children Act, section 4(a), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

## 2.6 Other Relevant Background Information

DEX is currently approved in the US for ICU sedation and for procedural sedation of non-intubated patients. DEX is approved in over 40 countries, with varying dose and duration restrictions. For example, the maximum maintenance dose is 0.7 mcg/kg/hr in the US, Canada, and Japan, 1 mcg/kg/hr in Australia, and 1.4 mcg/kg/hr in the European Union. Some countries, including the US, duration of infusion is limited to 24 hours, whereas other countries allow infusion for longer than 24 hours.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The Applicant's re-submission was considered acceptable for review on 2/15/13 once the missing datasets, narratives, and CRFs were received. However, the submission, after a sizeable number of amendments, remained difficult to review.

One major challenge stemmed from inconsistently defined variables across studies. For example, the applicant had a variable CMCONTRT that was derived differently for different studies but they concatenated the CMCONTRT variable in their ISS tables. However, pooling the data from different studies seems inappropriate unless CMCONTRT meant the same thing across studies.

Moreover, a concomitant medication flag was critical to this reviewer's assessment of medications administered during DEX, and therefore the Agency asked the Applicant to uniformly define CMCONTRT across studies. The applicant instead produced a new variable, CMRESEXT, with an unsatisfactory definition that failed to flag medications that were initiated prior to DEX. During a later teleconference, it was revealed that the Applicant would have to return to the source documents at the clinical sites to try and obtain the information that was required for creation of a variable that satisfied this reviewer's request that medications that were ordered prior to DEX and administered during DEX be eligible for consideration as rescue.

Another challenge was a lack of data standardization, leading to across many of the datasets that were pooled into the ISS datasets. For example, in order to determine which of the concomitant medications was administered as infusion, this reviewer had to manually select those medications that had, under dosing frequency, any of the following, all of which mean exactly the same thing:

- CI
- Other: continuous infusion
- Other: continuous
- Other: continuous drip
- Other: continuous gtt

The same dataset column also included the following slightly different but non-standarized, means of identifying an infusion:

- Other: continuous IV infusion per hour
- Other: mcg/kg/hr
- Other: prn and continuous infusion
- Other: PCA and continuous infusion

- Other: continuous- total daily dose
- Other: titrate(conc. 1mg/mg)
- Other: titrated
- Other: titrated( conc. 50 mcg/ml)
- Other: total daily dose-continuous

An additional challenge of a technical nature was finding the correct files. The Applicant's many amendments were often inappropriately indexed, leading to my review of an older file that had been revised but was not located in the proper locations within GlobalSubmit. In addition, the Applicant had originally submitted an interim and a final set of files for Study DEX-09-08. We asked for an integrated submission, which was provided, but ultimately none of the three files was complete and therefore, finding a file of interest often required looking through multiple folders because none three of the folders had all of the information for Study DEX-09-08.

The following outlines the series of amendments submitted by the Applicant and important interactions regarding submission integrity.

- On 1/2/13, Clin-Pharm requested the provision of a dataset that was absent actual data for study report DEX-08-01 as well as the exact dataset used for population pharmacokinetic analysis.
- On 1/8/13, an information request was sent to the applicant and responses were received on1/9/13 for the following:
    - Provision of all articles cited in the submission
        - Literature references were provided.
    - Locations of CRFs and narratives for all deaths
        - The applicant provided CRFs that had been omitted from the submission and also provided their locations; locations of narratives of some deaths were supplied and the applicant stated that narratives were not written for subjects in whom SAEs were not treatment emergent.
    - An explanation of the differences between interim and final modules for DEX-09-08
        - The applicant indicated that the interim report includes data for the first 30 subjects, the final report includes only the final six subjects, and the reports together represent a complete description of all DEX-09-08 subjects.
    - The location of or a rationale for not including an Integrated Summary of Efficacy (ISE) in the submission
        - The applicant did not include an ISE because it would have been redundant with the Comparison and Analyses Across Studies in Module 2.7.3.3. They also noted that the integrated efficacy data can be found in the end of text tables 10.1.1 to 14.1.

  - The rationale for the use of foreign data
    - Studies conducted were, per the applicant, under IND 32934, in compliance with 21 CFR 312 with standards of care equivalent to the US.
    - The applicant considers the foreign data generalizable and has not adjusted for center in the demographic analysis.
  - The completeness of the list of investigators included with form 3454
    - Per in applicant, the list includes investigators at all sites that enrolled subjects.
  - The location of the summary of available literature on the use of dexmedetomidine
    - The applicant limited their literature search to the pediatric population and referred to Module 5.4, which contains articles but no summary.
    - The applicant did not include the adult population in its review, and noted that they have complied with the PWR.
    - Through their pharmacovigilance program, the applicant monitors dexmedetomidine use and provide that information through Period Reports.
- On 1/17/13, a teleconference was held with the applicant and a follow-up information request sent on 1/22/13 for the following:
  - An integrated study report for DEX-09-08, which was added to the application on 2/6/13.
  - Many additional empty datasets
    - An administrative error was acknowledged by the applicant and datasets were added to the application on 1/24/13 to complete studies DEX-08-01 and CHOP.
    - The applicant was instructed to evaluate each study for completeness of datasets. They failed to identify and supply any datasets other than those named by the Agency as incomplete.
    - The applicant was requested to supply datasets for the W98-266 study but failed to do so.
  - Revised Integrated Summary of Safety to include W98-266 or an acceptable rationale for its exclusion. The rationale was provided on 1/30/13.
  - Narratives and case report forms for deaths, serious adverse events, and adverse dropouts, which were added to the application on 1/30/13.
- On 2/12/13, a teleconference was held with the applicant and a follow-up email sent requesting remaining empty datasets. On 2/13/13, three additional datasets were added to the application, and a follow-up teleconference was held with the applicant, confirming their receipt and the acceptability of the submission for filing.

- On 2/25/13, the Applicant provided study protocols, case report forms, informed consent forms, and individual patient listings that had been requested for the Office of Scientific Investigation in the filing letter.
- Around 2/28/13, the Agency requested modification of dataset ADINT.xpt to provide greater detail regarding reason for subject intubation.
    - On 3/4/13, the Agency received the modified dataset ADINT.xpt.
- On 3/15/13, the Agency received responses to other filing letter requests.
    - The Applicant indicated that a safety assessment based on all current worldwide knowledge of DEX was underway with a target submission date of 4/15/13. It was received on 4/16/13.
    - The Applicant reported updating all AE datasets to include all new adverse event variables that were published in the Dec. 2011 "Amendment 1 to the Study Data Tabulation Model (SDTM) v1.2 and the SDTM Implementation Guide: Human Clinical Trials V3.1.2".
    - The Applicant replaced some of image files with documents that can be text-searched.
    - The Applicant replaced a number of datasets that contained errors.
    - The Applicant provided one requested case report form and narrative summary.
- On 3/20/13, the Agency sent an information request to the Applicant with a request for response within one week; the Applicant provided no response. The Agency re-sent the same information request on 4/3/13, and followed it with an additional request sent on 4/10/13 and a response to both received on 4/19/13.
    - The Applicant provided new tables, like the original end of text ISE tables but based upon subjects who had received any DEX rather than the "efficacy evaluable" population, which had completed treatment with DEX.
    - The Applicant analyzed the incidence of rescue medication administration, considering medications administered after the start of study drug administration that might have a sedative effect and weren't being used for analgesia.
    - The Applicant corrected an error in Table 8 of the DEX-08-05 CSR.
    - The Applicant submitted narrative summaries for eight subjects who were early discontinuations and for 48 subjects who had, as a rationale for stopping the study drug, "other".
    - The Applicant explained that reasons for study drug discontinuation were not recorded in DEX-08-01 and CHOP, and therefore, these fields are blank in the ADSL.xpt file.
    - The Applicant explained that the CM.xpt file includes many instances of midazolam administration that were not captured in ADMI.xpt because ADMI.xpt was derived from the rescue medication eCRF for all studies except CHOP.
    - The Applicant explained that one subject had no age in the demographics dataset because the site's Research Ethics Board did not allow entry of the subject's exact birth day.

  - The Applicant updated the ISS ADSL.xpt file for Supplement 22 to indicate, for all studies rather than select studies, whether subjects had cardiopulmonary bypass.
  - Because the Applicant had derived the variable CMCONTRT differently between studies, a new field was created and defined as all medications that began between the start of study drug administration and extubation or by end of study drug administration, whichever comes first.
  - The Applicant informed us that the administrative reason behind the discontinuation of DEX-09-08 was to ensure a data cutoff that would support compilation of a clinical study report and earlier progression to a Pediatric Written Request Supplement.

- On 5/8/13, the Agency sent an information request to the Applicant with a request for a teleconference to discuss responses. The teleconference occurred on 5/9/13, and later that day a written summary of responses was received. The Applicant's written summary did not completely capture the discussion, and the Agency added a document to DARRTs reflecting the discussion during the teleconference.
  - The Applicant informed the Agency that vital signs were recorded as defined in the protocol, and not necessarily during adverse events, but rather at defined points in time relative to (1) DEX infusion initiation and termination as well as (2) administration of rescue medication.
  - The Applicant acknowledged that a narrative summary in the submission "somewhat vague" and explained that the subject of the narrative did not have an adverse event because the principle investigator did not consider the low blood pressure an adverse event, despite it being a reason for study drug discontinuation.
  - The Applicant informed the Agency that in the concomitant medications datasets, each entry represents an order. When midazolam was administered, information should have been captured on the rescue midazolam CRF. However, for medications other than midazolam, information about timing, dosing, and changes in infusion rates were not collected. In order to obtain this information, the Applicant stated they would have to look into the source documents at the clinical sites.
  - The Applicant informed the Agency that they recorded only dates of administration and not times, with a flag for medications that were administered prior to the study drug. For details regarding the timing of other medications, the Applicant would have to look into the source documents.

Audits by the Office of Scientific Investigations (OSI)

The clinical investigator sites chosen for inspection (Drs. Chrysostomou, Hammer, and Zuppa) were selected primarily based on enrollment characteristics. These sites had high enrollment numbers or high percentages of enrolled subjects within their study. The OSI reports were not available at the time of this review, and will be incorporated into the review by the Clinical Team Leader. However, the Division has been preliminarily informed that the Hammer and Chrysostomou site inspections have been completed and both had some 483 findings, or minor deficiences, and a preliminary assessment of Voluntary Action Indicated.

- Dr. Chrystostomou is an investigator at the Children's Hospital of Pittsburgh who enrolled subjects in two studies, namely DEX-09-08 (Site #100) and DEX-11-01 (Site #01).

- Dr. Gregory Hammer is an investigator (Site #20) in study DEX-08-05 at the Stanford University Medical Center.

- Dr. Zuppa is an investigator a single-site study, CHOP, at the Children's Hospital of Philadelphia.

## 3.2 Compliance with Good Clinical Practices

According to the applicant, studies DEX-08-05, DEX-09-08, DEX-11-06, CHOP, DEX-08-01, and DEX-11-01 were planned and conducted under the rules of Good Clinical Practice, and the original protocol and amendments as well as informed consent and subject information and advertising, as relevant, were approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The above-listed studies were reportedly conducted in accordance with the protocols, ICH guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles having their origin in the Declaration of Helsinki.

According to the applicant, the investigator or their representative explained the nature of the study to the parents or legally acceptable representative and answered all questions, and the informed consent statement was reviewed and signed prior to performing any study-related screening procedures on the subject in the case of all studies listed above as well as W98-266.

### 3.3 Financial Disclosures

Individual financial disclosures were not submitted for any studies. Hospira instead submitted a financial certification (Form 3454) stating that the listed clinical investigators hadn't any financial arrangement with the sponsor whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study, nor had these clinical investigators a proprietary interest in the product or significant equity interest in the sponsor. The applicant also certified that the investigators had not been recipients of significant payments of other sorts. When queried in an information request on 1/8/13, the applicant noted that the list of investigators included all who had enrolled subjects.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

There is no need for data pertaining to clinical manufacturing and controls for this application.

### 4.2 Clinical Microbiology

There is no need for data pertaining to clinical microbiology for this application

### 4.3 Preclinical Pharmacology/Toxicology

DEX is a sedative of particular interest in pediatrics because, based on our recent understanding, it is alone in not causing apoptosis in the developing brain. However, preliminary discussions of this supplement have revealed that the Applicant submitted two non-clinical studies that did not satisfactorily confirm that DEX lacks neurotoxicity, as the studies did not gather all the desired information, and revealed some previously unknown neuron degeneration in the somatosensory cortex.

The rat study evaluated neural degeneration within several areas of the brain, comparing DEX at different doses to saline (placebo) and ketamine (positive) controls. Whereas the expectation was for no increase in apoptosis, DEX appeared to induce a higher incidence of degeneration among neurons of the somatosensory cortex. This study was limited in that it did not conform with Good Laboratory Practice, some DEX data are missing, and fewer than the desired number of slices were analyzed.

The monkey study shared some of the limitations of the rat study, such as non-conformance with Good Laboratory Practice and limited slices. Of greatest concern is the evaluation of only the prefrontal cortex, particularly given the rat data, which suggested that degree of neural degeneration with DEX exposure differed in different areas of the brain. Within the prefrontal cortex, the only area of assessment, a possible small increase in neural degeneration with DEX over saline control was observed.

## 4.4 Clinical Pharmacology

Preliminary discussion of the supplement did not reveal any items of concern from the Clinical Pharmacology reviewer's perspective. The reviewer reported that DEX pharmacokinetics had been adequately characterized in all pediatric age groups, with linear kinetics and non-accumulation in renal impairment.

Also discussed was the possibility (b) (4) .

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

**Table 2 Clinical Studies and Trials Considered in the Review of NDA 021038 S021 & 022**

| Study Name | Dates | Design | Treatment | | Subject No. | Age | Location of Sites (N – total # sites) | Primary Endpoint | Data |
|---|---|---|---|---|---|---|---|---|---|
| | | | µg/kg load | µg/kg/hr infusion | | | | | |
| Primary Trials | | | | | | | | | |
| DEX-08-05 | 1/10 to 1/11 | DB with respect to DEX dose | 0.2 | 0.2 | 89 | 1 mo – 16 yrs | U.S., Canada (29) | Percent of subjects not receiving rescue midazolam | Safety Efficacy |
| | | | 0.3 | 0.5 | | | | | |
| | | | 0.5 | 0.5 | 86 | | | | |
| | | | 0.6 | 0.6 | | | | | |
| DEX-09-08 | 7/10 to 6/11 | Open | 0.05 | 0.05 | 14 | 28 wks – 44 wks | U.S. (11) | Incidence of midazolam rescue | PK Safety Efficacy |
| | | | 0.1 | 0.1 | 14 | | | | |
| | | | 0.2 | 0.2 | 8 | | | | |
| DEX-11-06 | 3/12 to 5/12 | Open | 0.2 | 0.2 | 6 | 28-35wks | U.S. (3) | Frequency of midazolam | Safety Efficacy |
| Supportive Studies | | | | | | | | | |
| CHOP | 10/04 to 12/06 | Open | 0.35 | 0.25 | 12 | >1 mo - <2 yrs | U.S. (1) | PK/PD | PK PD Safety |
| | | | 0.7 | 0.5 | 12 | | | | |
| | | | 1 | 0.75 | 14 | | | | |
| DEX-08-01 | 11/08 to 4/10 | Open | 0.25 | 0.5 | 16 | 2 yrs – 16 yrs | U.S., Guatemala (6) | PK/PD | PK PD Safety |
| | | | 0.5 | 0.4 | 14 | | | | |
| | | | 1 | 0.7 | 15 | | | | |
| | | | 1 | 2 | 14 | | | | |
| DEX-11-01 | 6/11 to 8/11 | Open | 0.7 | 0.5 | 2 | 12 mo – 23 mo | U.S. (1) | PK/PD | PK PD Safety |
| | | | 1 | 0.75 | 3 | | | | |
| W98-266 | 5/99 to 9/01 | Open | 0.33 | n/a | 8 | 2 yrs – 12 yrs | Canada, South Africa (2) | PK/PD | PK PD Safety |
| | | | 0.67 | n/a | 8 | | | | |
| | | | 1 | n/a | 8 | | | | |

## 5.2 Review Strategy

A number of sections were deleted from the Clinical Review Template because they were not relevant to the review of this supplement. The deleted sections are listed below:

Recommendations Sub-Sections

- 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies
- Recommendations for Postmarket Requirements and Commitments

Clinical Pharmacology Sub-Sections:

- 4.4.1 Mechanism of Action
- 4.4.2 Pharmacodynamics
- 4.4.3 Pharmacokinetics

Safety Sub-Sections:

- 7.4.5 Special Safety Studies/Clinical Trials
- 7.4.6 Immunogenicity
- 7.6.1 Human Carcinogenicity
- 7.6.2 Human Reproduction and Pregnancy Data
- 7.6.3 Pediatrics and Assessment of Effects on Growth
- 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound
- 7.7 Additional Submissions / Safety Issues

Postmarket Experience:

- 8 Postmarket Experience

Appendix:

- 9.1 Literature Review/References
- 9.2 Labeling Recommendations
- 9.3 Advisory Committee Meeting

## 5.3 Discussion of Individual Studies/Clinical Trials

*Primary Trials*

**Study DEX-08-05**

A Phase III, Randomized, Double-Blind, Dose-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Dexmedetomidine in Intubated and Mechanically Ventilated Pediatric Intensive Care Unit Subjects.

Objectives

The objectives were:

- To characterize the loading and maintenance dosing of DEX by age group and overall medical condition of pediatric subjects
- To evaluate the safety and efficacy of loading and maintenance infusions for sedation in initially intubated and mechanically ventilated PICU subjects
- To explore the exposure-response relationship between dose of DEX and clinical measures of sedation and safety

Design

A Phase 3, multicenter, prospective, randomized, double-blind, dose-controlled study. Enrolled subjects were randomized into one of two treatment groups to receive either high dose or low dose DEX, and were stratified according to the presence or absence of cardiopulmonary bypass.

**Table 3 DEX-08-05 Schedule of Activities**

| Procedure | Screening (No more than 14 days before study drug administration) | Baseline (prior to study drug infusion) | Infusion of DEX (minimum 6 hrs up to 24 hrs) | 24hrs post DEX Stop | Within 24 hrs of discharge | Post-dose Day 28 (± 5 days) |
|---|---|---|---|---|---|---|
| Informed Consent[1] | X | | | | | |
| Demographics | X | | | | | |
| Medical History | X | | | | | |
| Physical Examination[2] | X | X | | X | X | |
| Inclusion/Exclusion | X | | | | | |
| Reason for Intubation | X | | | | | |
| ASA Classification | X | | | | | |
| Vital Signs (SBP, DBP, HR, RR, $SpO_2$, ($TcCO_2$ and/or ABG, if available)[3] | X | X | X | X | X | |
| Core Body Temperature[4] | X | X | X | X | | |
| Body Weight[2,5] | X | X | | X | X | |
| 12-Lead ECG/Continuous Cardiac Monitoring[6] | X | X | X (continuous) | X | | |
| Laboratory Evaluation (chemistry, hematology & urinalysis)[7] | X | X | | X | X | |
| Cortisol/ACTH Stimulation[8] | X | X | X | | | |
| Pregnancy Test[9] | X | | | | | |
| Randomization | | X | | | | |
| Ventilator Setting[10] | | X | X | X | | |
| Input/Output Fluid Volumes | | X | X | | | |
| University of Michigan Sedation Scale[11] | | X | X | | | |
| Paradoxical Agitation Reactions | | | X | X | | |
| Study Drug Administration | | | X | | | |
| Morphine Use[12] | | | X | | | |
| Midazolam Use[12] | | | X | | | |
| Fentanyl Use[12] | | | X | | | |
| Concomitant Medication[13] | X | X | X | X | | |
| Adverse Events | X | X | X | X | X | X |
| Phone Follow-up | | | | | | X |

Note: <1-hour increments were within ±1 minute and ≥1-hour increments were within ±5 minutes. Footnotes are on the following page

Footnotes for **Error! Reference source not found.**:

1. Informed consent was obtained before any study related procedures were performed.
2. Physical examination was performed a)For all subjects, during screening (or prior to surgery), b)For subjects who were post-cardiac bypass an additional physical exam was to be performed during baseline and c)For all

subjects, in close proximity to hospital discharge or anytime between Days 5-7 whichever occurred first. Weight and height were also obtained.

3. Vital signs were obtained at screening. For a loading dose, vital signs were obtained at 5, 10 and 15 minutes (if applicable for a 20 minute load) after start of study drug load. Following commencement of the continuous study
drug infusion vital signs were obtained at 15 and 30 minutes, and 1, 4, 8, and 12 hours for the first 24 hours and, thereafter, every 4 hours until the end of the maintenance infusion. Vital signs were monitored immediately prior
to maintenance infusion discontinuation, hourly after discontinuation of study drug for 6 hours and every 4 hours for the remainder of the follow-up period, and also within 24 hours of discharge or on Day 5-7.
4. Core body temperature was collected at screening, baseline and then every 12 hours during DEX administration, immediately preceding discontinuation of DEX, and at the end of the 24-hour follow-up period.
5. Actual body weight, NOT lean body weight. Baseline weight was to be used to determine study drug infusion rate.
6. The screening ECG and labs were obtained up to 14 days prior to first dose of study drug. For postoperative cardiac surgery subjects, the baseline labs and 12-lead ECG were to be obtained POSTOPERATIVELY, but no
greater than 90 minutes following the start of study drug. Continuous cardiac monitoring occurred while on study drug and a daily 12-lead ECG was performed for all subjects. A 12-lead ECG was obtained 24 hours after
discontinuation of study drug infusion or prior to discharge, whichever came first.
7. Standard of care labs and study labs were reviewed throughout the study for AEs. Labs collected for standard of care anytime within 24 hours of hospital discharge or between days 5-7 (whichever came first) were recorded into the eCRF. The baseline labs for postoperative cardiac surgery subjects were to be obtained postoperatively, but no greater than 90 minutes following the start of study drug.
8. In a subset of sites a baseline cortisol level was obtained for all diagnoses except CPB prior to the start of DEX administration. In s/p CPB subjects, this blood draw was obtained postoperatively, but not greater than 90 minutes following the start of DEX administration; this could done in conjunction with other baseline labs drawn postoperatively. Following discontinuation of the infusion of study drug an ACTH-stimulation test was performed, where a cortisol level was drawn in conjunction with the administration of ACTH. At 60 minutes following the administration of ACTH, a repeat cortisol level was obtained.
9. Either urine or serum for females of childbearing potential.
10. Ventilator settings were obtained every 4 hours.
11. If loading, UMSS score was to be documented just immediately before loading and at 5, 10, and 15 minutes (if load continued 20 minutes) during the load. At the start of maintenance infusion, UMSS score was to be documented at 5, 10, 15, 30 minutes, 1, 4, 8 and 12 hours and then every 4 hours after the start of the maintenance infusion, and also immediately before and after 5 minutes after any titration of study drug, and immediately before and after 5 minutes following administration of MDZ. If fentanyl or morphine was given as a continuous infusion, UMSS scores were obtained immediately before and 5 minutes after. A UMSS score was documented for non-pharmacologic intervention (e.g., swaddling, cuddling, rocking) immediately before and within 5 minutes after the intervention.
12. DEX could be titrated up and MDZ, morphine, or fentanyl could be used in instances where severe anxiety or agitation was anticipated (e.g., prior to a stressful or painful procedure such as suctioning or chest tube removal). Note that the DEX infusion had to be titrated up either prior to or simultaneously with the administration of MDZ, and prior to the administration of fentanyl or morphine.
13. Concomitant medications collected for 48 hours prior to start of study drug infusion period and for 24 hours after discontinuation.

Treatments and Interventions

175 subjects were enrolled and randomized into low-dose and high-dose treatment groups; within each group, the loading and maintenance doses were stratified according to the presence or absence of cardiopulmonary bypass (CPB).

**Table 4 DEX-08-05 Treatment Groups**

| Diagnosis | Group 1<br>Low dose DEX | Group 2<br>High dose DEX |
|---|---|---|
| s/p CPB | Optional loading dose<br>0.2 mcg/kg | Optional loading dose<br>0.5 mcg/kg |
| | Maintenance dose titration range<br>0.025 – 0.5 mcg/kg/hr | Maintenance dose titration range<br>0.1 – 0.7 mcg/kg/hr |
| All other diagnoses | Optional loading dose<br>0.3 mcg/kg | Optional loading dose<br>0.6 mcg/kg |
| | Maintenance dose titration range<br>0.05 – 0.5 mcg/kg/hr | Maintenance dose titration range<br>0.2 – 1.4 mcg/kg/hr |

Sedation level was assessed using the University of Michigan Sedation Scale (Table 5), and when additional sedation was deemed necessary, the DEX dose was titrated upwards; subjects were reassessed thereafter for the need for rescue midazolam. When needed, midazolam was dosed according to its label; subjects up to five years of age received 0.05 to 0.1 mg/kg, six to twelve years of age received 0.25 to 0.05 mg/kg, and older than twelve received 1 to 3 mg.

**Table 5 University of Michigan Sedation Scale (UMSS)**

| Clinical score | Level of sedation |
|---|---|
| 0 | Awake/Alert |
| 1 | Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sounds |
| 2 | Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation |
| 3 | Deeply sedated: deep sleep, arousable only with significant physical stimulation |
| 4 | Unarousable |

Subjects were also eligible for opioid therapy. Infusions initiated prior to randomization were continued as needed during study drug administration. In addition, subjects could receive fentanyl or morphine for persistent pain after initial treatment with an increased DEX infusion rate. In addition, all medications within 48 hours prior to DEX initiation were to be recorded, along with date and time of administration, exact dosages, route of administration, and reasons for use.

Prohibited medications during DEX infusion included the following:

- Sedatives and analgesics other than DEX, midazolam, morphine, or fentanyl.
  - Acetaminophen was permitted only as an antipyretic
- Continuous infusion of neuromuscular blocking medications
- Medications contraindicated with the use of DEX, midazolam, morphine, or fentanyl
- Alpha$_2$-agonists and –antagonists other than DEX

Population

The study population consisted of initially intubated and mechanically ventilated pediatric subjects, aged 1 month through <17 years; if premature and less than three months of age, subject age was corrected for gestational age. Subjects were also grouped according to age <24 months or ≥24 months.

Sample Size:
The Applicant based sample size upon a chi-square analysis for two proportions, 80% power, alpha=0.05, assuming an incidence of rescue midazolam of 62-77% in the high dose group and 17-19% higher incidence of rescue midazolam in the low dose group.

- Planned: 175 subjects at approximately 40 investigative sites.
- Analyzed: 175 subjects for safety, 164 for efficacy.

Inclusion Criteria:

(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) classification of 1, 2, 3, or 4.
(4) A UMSS score of 1, 2, 3, or 4 at the start of infusion of study drug.
(5) A dose had been established for this subject's age.
(6) If female, subject was non-lactating and was either:

- Not of childbearing potential, defined as pre-menarche, or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy.
- Of childbearing potential but was not pregnant at time of baseline.

(7) Subject's parent(s) or legally acceptable representative had/have voluntarily signed and dated the informed consent document approved by the Institutional Review Board (IRB). Assent was obtained where age-appropriate and according to state regulations.

Exclusion Criteria:

(1) Pediatric 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:
    a. Age 1 month to ≤6 months old: systolic BP (SBP) <60 mmHg
    b. Age >6 months to <2 years old: SBP <70 mmHg
    c. Age >2 to <12 years old: SBP <80 mmHg
    d. 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 beats per minute (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) Alanine aminotransferase (ALT/ serum glutamic-pyruvic transaminase [SGPT]):
    a. 1 month to 12 months old: >165 units/liter (U/L)
    b. >12 months to <17 years old: ≥100U/L

    Note: Subjects could be re-screened up to 6 hours prior to study drug infusion (not including subjects undergoing cardiac surgery with CPB).

(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.
(9) Subjects with immobility from neuromuscular disease, paralysis from administration of neuromuscular blocking (NMB) agents, spinal cord injury above T5 or subjects with muscle weakness from congenital or systemic medical illness etiologies.

Note: 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.

(10) Subjects had received another investigational drug or device within the past 30 days.
(11) Subjects had received DEX in a previous clinical investigational trial within the previous 12 weeks.
(12) Subjects who, in the opinion of the Investigator, had any other condition where the risks of DEX would be expected to outweigh its benefits (e.g., cardiogenic shock on >2 vasopressors).
(13) Subjects who would require alpha-2 agonists/antagonists within 48 hours prior to baseline. (See Appendix C of the protocol for a listing of alpha-2-agonists and antagonists.)

Endpoints and Analyses

Analysis Populations:

- Intent-to-Treat Population (ITT): All randomized subjects.
- Safety Evaluable Population (SE): A subset of ITT population that received any study drug. Used in all safety reporting and analyses.
- Efficacy Evaluable Population (EE): All subjects randomized to study drug that received randomized study drug for at least 6 hours. Used for efficacy analysis.

Primary Endpoint Analysis:
The primary efficacy variable was to be summarized for each treatment group using descriptive statistics. In addition, the difference between treatment groups was to be assessed as risk differences for 2x2 tables with 95% confidence interval with a continuity correcting using PROC FREQ in SAS. Finally, differences between treatment groups adjusting for underlying condition or age group will be assessed using Mantel-Haenszel (MH) test in PROC FREQ.

Secondary Endpoints:

- Absolute time and percentage of time on study drug that the subject is in a UMSS score range of 1-3 while intubated
- Absolute time and percentage of time on study drug that the subject is 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
- Time to extubation

Changes in Protocol or Planned Analysis

Protocol Amendments:
Changes to the protocol were made twice during the study. The final amended clinical study protocol was compiled on 7 Jun 2010.

*1st Amended Clinical Study Protocol (22 Sept 2009)*
Most of the changes were clarifications that did not affect the conduct of the study. The Amendment's Appendix H consists of a list of specific changes. The protocol changes, as summarized by the Applicant, follow:

1. Where appropriate, throughout the protocol the word subjects was substituted for patients.
2. Change Hospira staff members where applicable.
3. Clarify age definition of premature infants.
4. Clarify that the informed consent must be signed prior to performing any Screening procedures.
5. Addition of new Exclusion Criteria to ensure facilities have the appropriate infusion pumps to deliver the potentially low volumes needed in this population.
6. Clarify time of collection of vital signs, physical exam, electrocardiogram (ECG), laboratory procedures, core temperatures and University of Michigan Sedation Scale (UMSS) variables.
7. Specify the loading dose and maintenance dose titration ranges for this study based upon subject age.
8. Clarify how dosing guidance will be obtained in the future for the ≥ 24 months to <17 year old subjects.
9. Add UMSS criteria of 1**,** 2, 3 or 4 for study entry.
10. Clarify the inclusion criteria based upon age.
11. Clarify the exclusion criteria based upon age.
12. Clarify the exclusion criteria for hypotension.
13. Clarify the exclusion criteria for bradycardia.
14. Clarify that non-cardiopulmonary bypass (CPB) subjects may be rescreened for up to 6 hours prior to study drug infusion for serum glutamine pyruvic transminase (SGPT/ALT) levels.
15. Clarify the enrollment eligibility of subjects who received neuromuscular blocking (NMB) agents.
16. Stated subjects may not have received dexmedetomidine (DEX) in another investigational clinical trial within the last 30 days.
17. Clarify when UMSS should be recorded in relation to midazolam dosing.
18. Clarify that sedation control should first be attempted with DEX then with rescue agents.
19. Clarify the manner in which subjects may be converted to an alternative sedative.
20. Clarify the collection period for adverse events (AEs).

21. Clarify the collection period for concomitant medications.
22. Clarify the methods for obtaining core body temperature.
23. Add justification for future dosing of subjects ≥ 24 months to < 17 years
24. Add study drug preparation for a high and low dose DEX drug concentration in order to maintain blinding of the infusion rate.
25. Include the use of an Internet Web-Based Randomization System (IWRS) system in this study.
26. Change the review cycle of the Data and Safety Monitoring Board (DSMB) and the criteria for progressing to the dosing beyond 24 hours.
27. Clarify that laboratory data from this study will not be electronically transferred to Hospira or its designee.
28. Throughout the protocol the length of dosing was changed to include a staged approach beginning at 24 hours and then progressing up to 1 week pending approval of the DSMB.
29. Add measurement of cortisol levels at baseline and adrenocortiocotropic hormone (ACTH) stimulation testing.
30. Include that specific AEs (agitation, cardiac dysrhythmias and acute respiratory distress syndrome) should be monitored.
31. Add a study visit at Day 7 or at the time of discontinuation.
32. Add a telephone follow-up at Day 28.
33. Add daily lab reviews for potential AEs.
34. Clarify that the collection of input/output levels is to be done daily.
35. Include recommendation that subjects on open-label DEX do not receive a loading dose, and note that ultimately the decision is up to the Investigator.
36. Add missing abbreviations to the abbreviation table.
37. Delete Appendices D through G (dose tables), to be provided in the Pharmacy Manual, to help ensure the blind.
38. Safety contact information updated.

*2nd Amended Clinical Study Protocol (7 Jun 2010)*

Most of the changes were clarifications that did not affect the conduct of the study. The Amendment's Appendix H consists of a list of specific changes. The reasons for protocol changes, as summarized by the Applicant, follow:

1. Introduce abbreviations where appropriate throughout the protocol.
2. Add missing abbreviations to the abbreviations table.
3. Change Hospira staff members where applicable.
4. Update the inclusion criteria for means of intubation and time period of mechanical ventilation.
5. Clarify the exclusion criteria for hypotension and bradycardia.
6. Modify the variables in screening assessments to include weight.
7. Add concomitant medications and laboratory evaluations to the list of post-infusion period assessment variables.

8. Clarify that for cardiopulmonary bypass (CPB) subjects, baseline cortisol level blood draws, laboratory blood draws, and electrocardiogram (ECGs) must be obtained postoperatively, but no greater than 90 minutes (mins) following study drug administration.
9. Change the maximum treatment time from 7 days to 24 hours (hrs), where appropriate, throughout the protocol.
10. Omit information pertaining to treatment stages, as there will no longer be different stages of treatment.
11. Omit background information regarding treatment duration longer than 24 hrs.
12. Clarify the methods by which dexmedetomidine (DEX) may be administered.
13. Clarify precautions of co-administering other medications with DEX.
14. Clarify that if additional sedation or treatment of pain/discomfort is required, it is advised that DEX study drug should be attempted as first line therapy prior to the use of rescue therapy.
15. Clarify the concentration by which DEX may.be increased for the treatment of pain/discomfort.
16. Clarify that the decision to use rescue therapy is left to the discretion of the Investigator.
17. Correct dose recommendations for rescue therapy fentanyl and morphine.
18. Clarify the manner in which subjects may be converted to an alternative sedative.
19. Clarify that subjects requiring deeper sedation (University of Michigan Sedation Scale [UMSS] of 4) or continuous neuromuscular blockade will be discontinued from the study.
20. Clarify time of collection of vital signs, physical exam, ECG, laboratory procedures, core temperatures, and UMSS variables.
21. Clarify that all serious adverse event (SAEs) must be followed to resolution or until the SAE is determined by the Investigator to no longer be clinically significant.
22. Add that SAEs reported during the Post-Dose Day 28 follow-up call will also be reported.
23. Update contact information for SAE reporting.
24. Clarify that the Data and Safety Monitoring Board (DSMB) will meet at prescribed intervals according to the DSMB Charter Agreement.
25. Clarify that the DSMB will not have knowledge of the population being studied or regulatory responsibilities for the trial.
26. Correct clerical errors.
27. Update references.
28. Added Appendix I [Dose Rationale]

Changes in Statistical Analysis Plan

The final Statistical Analysis Plan (SAP), dated 11 Feb 2011 and changed 18 July 2011, is provided in Appendix 16.1.9. The list of SAP changes, as provided by the Applicant, follows:

1. ASA Classification was added into baseline assessment.
2. The 95% confidence interval was removed from the primary efficacy as risk differences.
3. ASA Classification was added into primary efficacy analysis and summarized by the more critically ill group of P3, P4 and the less critically ill group of P1, P2.
4. ASA Classification was added into study drug exposure analysis and summarized by the more critically ill group of P3, P4 and the less critically ill group of P1, P2.
5. Follow-up data were summarized and listed for:
    - Phone follow-up events
    - Adverse events occurred or continued during follow-up visit.
6. CRF data were not listed to be added in the appendix 16.2.
    - Intubation
    - Painful procedure
7. Derived variables were added in the appendix 16.2
    - Time to extubation
    - Time to the first dose of rescue medication for Sedation and Analgesia
    - Absolute time and percentage of time on study drug that subject was in the target sedation range (UMSS 1-3)
    - Absolute time and percentage of time on study drug that subject was out of the target sedation range
    - Total amount and the weight adjusted total amount (per kg) of rescue medication for sedation and analgesia during study drug infusion

**Medical Reviewer Comments:**
Of the studies within the supplement, DEX-08-05 was unique because it was the only clinical trial with blinding (b) (4). Subjects included in the study ranged from 1 month to < 17 years of age, and therefore (b) (4) assessments and dosing protocols were the same for a wide range of subject ages.

DEX-08-05 was also unique in that it stratified subjects according to presence or absence of CPB, as the DEX requirement was expected to be lower in subjects who received CPB.

One aspect of the protocol that may have contributed to its failure to demonstrate efficacy was the heterogeneity of dosing among subjects within a dose group. The

range of allowed doses within a treatment group was so large that after titration, subjects within the same dose group could have as much as a 20-fold difference in DEX dose. Also increasing the dosing heterogeneity among subjects within the same group was the option for investigators to administer a loading dose of DEX; while the dose was prescribed, its administration was optional and the investigator could also dictate the loading period within a range of 10-20 minutes.

The wide titration ranges led to significant overlap between the groups, and likely contributed to the trial's failure to demonstrate efficacy. For example, after dose titration, subjects in the CPB low dose group could receive five times the infusion rate of DEX as subjects in the CPB high dose group.

**Study 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

Objective

To characterize the safety, efficacy and PK of DEX administered as an intravenous (IV) loading dose followed by a continuous IV infusion in neonates, ages ≥ 28 weeks through ≤ 44 weeks gestational age.

Design

This was a Phase II/III open-label, multicenter, safety, efficacy, and PK study of DEX in neonates. The study population consisted of initially intubated and mechanically ventilated male and female neonate subjects, age ≥ 28 weeks to ≤ 44 weeks gestational age, who required sedation in an intensive care setting for a minimum of 6 hours. Subjects were divided into 2 groups based on age. Age group I consisted of premature neonates, ≥ 28 weeks to < 36 weeks, and age group II consisted of term neonates ≥ 36 weeks through ≤ 44 weeks gestational age. Within each group, there were three escalating dose levels.

**Table 6 Schematic Diagram of Study DEX-09-08 Design**

| | **DEX Infusion Period** | | **Post-infusion period (24 hours)** | **Up to discharge or study day 7** |
|---|---|---|---|---|
| Level 1 | DEX load 0.05 mcg/kg over 10 or 20 min | DEX maintenance 0.05 mcg/kg/hr (at least 6 and up to 24 hours) | | |
| | | N-PASS with rescue sedation (MDZ) or rescue analgesia (morphine or fentanyl) | | |
| | | PK measures | | |
| | | Efficacy and safety measures | Efficacy and safety measures | Safety Monitoring |
| Level 2 | DEX load 1.1 mcg/kg over 1.2 10 or 20 min | DEX maintenance 0.1 mcg/kg/hr (at least 6 and up to 24 hours) | | |
| | | N-PASS with rescue sedation (MDZ) or rescue analgesia (morphine or fentanyl) | | |
| | | PK measures | | |
| | | Efficacy and safety measures | Efficacy and safety measures | Safety Monitoring |
| Level 3 | DEX load 0.2 mcg/kg over 10 or 20 min | DEX maintenance 0.2 mcg/kg/hr (at least 6 and up to 24 hours) | | |
| | | N-PASS with rescue sedation (MDZ) or rescue analgesia (morphine or fentanyl) | | |
| | | PK measures | | |
| | | Efficacy and safety measures | Efficacy and safety measures | Safety Monitoring |

DEX = dexmedetomidine, N-PASS = Neonatal Pain, Agitation, and Sedation Scale; MDZ = midazolam; PK = pharmacokinetics
Source: 5.3.5.1 DEX-09-08 protocol Figure 1, p. 84

Treatments and Interventions

Dexmedetomidine was administered as a 2-stage infusion. Infusions were fixed and administered for at least six and no more than 24 hours post-operatively. Dose groups are outlined in Table 7 below.

**Table 7 DEX-09-08 Dosing Groups**

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

Source: 5.3.5.1 DEX-09-08 protocol Table 1, p. 87

Rescue Medications:
Rescue medication was administered as needed for sedation (MDZ) and pain (fentanyl or morphine), during DEX administration based on results of the N-PASS sedation/pain scale. Rescue therapy was indicated when the total N-PASS score was > 3, and the selection of sedative rescue or analgesic rescue was at the discretion of the Investigator. For any administration of rescue therapy, the date, time, and exact dose of each rescue and the reason for use were recorded in the eCRF.

*Midazolam*
If, in the opinion of the Investigator or designee, the subject was not adequately sedated or if the Investigator desired a deeper level of sedation, MDZ could be administered. Rescue MDZ was administered based on labeling for pediatrics at a recommended dose of 0.05 to 0.15 mg/kg per dose. The package insert recommends 2 to 3 minutes between doses; however, this was left to the discretion of the Investigator. The N-PASS score was obtained prior to the administration of rescue medication and within 5 minutes after administration of MDZ.

*Fentanyl*
If, in the opinion of the Investigator or designee, the subject was in pain and rescue analgesia was required, the subject could receive fentanyl (0.5 to 2 mcg/kg bolus or 1 to 2 mcg/kg/hr continuous infusion). For every bolus dose of fentanyl that was given, a justification fitting into at least one of the following categories had to apply and be recorded in the eCRF:

- N-PASS total score > 3;
- Subject's stress was not relieved with rescue MDZ;
- Presence of pain based on the Investigator's or designee's judgment;

- Anticipated pain prior to an intervention (e.g., blood draw, suctioning).

For continuous infusions of fentanyl, the N-PASS was recorded immediately prior to initiating the continuous infusion. Note: any titration to an analgesic continuous infusion necessitated that the N-PASS be obtained immediately before and within 5 minutes following the titration.

*Morphine*
If, in the opinion of the Investigator or designee the subject was in pain and rescue analgesia was required, the subject could receive morphine as a bolus or continuous infusion (0.025 to 0.1 mg/kg bolus or 0.01 to 0.02 mg/kg/hr continuous infusion). For every bolus dose of morphine that was given, a justification fitting into one of the following categories was used and recorded in the eCRF:

- N-PASS total score > 3;
- Subject's stress was not relieved with rescue MDZ;
- Presence of pain based on the Investigator's or designee's judgment;
- Anticipated pain prior to an intervention (e.g., blood draw, suctioning).

For continuous infusions of morphine, the N-PASS was recorded immediately prior to initiating the continuous infusion. Note: any titration to an analgesic continuous infusion necessitated that the N-PASS be obtained immediately before and within 5 minutes following the titration. The concurrent utilization of bolus and continuous infusion of opiates was allowed; however, it was recommended that the continuous infusion dosage be reduced. Other comfort measures (e.g., rocking, swaddling, pacifiers) were recorded in the eCRF.

At any time clinically indicated (e.g., subject discomfort despite maximum doses of rescue), or at the discretion of the Investigator or designee, the subject could be converted to an alternative sedative or analgesic therapy that was not permitted within this protocol. If a subject was converted to an alternative sedative and/or analgesic therapy, DEX was to be discontinued and the subject would have been considered a premature termination from the study. Post-infusion PK samples were obtained and 24-hour follow-up procedures were to be initiated at the time DEX was discontinued.

Concomitant Medications:
Use of the following drugs was prohibited during the DEX infusion period:

- Sedatives and analgesics other than DEX, MDZ, morphine, or fentanyl. Acetaminophen was permitted only as an anti-pyretic during DEX infusion. Use of non-steroidal anti-inflammatory drugs were allowed for the management of patent ductus arteriosus, but must have been appropriately recorded in the eCRF.
- Any continuous infusion of neuromuscular blocking agents or repeated use of a neuromuscular blocking agent that would preclude the Investigator from reliably obtaining the N-PASS measure while the subject was on DEX. If a neuromuscular blocking agent was used (i.e., surgical intervention), a 6 hour wash-out period or

pharmacological reversal was necessary prior to commencement of DEX. The periodic bolus dosing of NMB agents to facilitate painful interventions was allowed but had to be appropriately recorded in the eCRF.
- Any drugs contraindicated with the use of DEX, MDZ, morphine, or fentanyl.
- Alpha-2 agonists/antagonists other than DEX (see Appendix C of the protocol [Appendix 16.1.1]).
- Anesthetic or analgesic agents administered via an epidural or spinal route during the DEX infusion period.

Populations

Sample Size Determination:
The sample size was based upon a pairwise comparison between the low dose group and the high dose group. It was expected that 90% of subjects in the lowest dose group would require rescue medication use for sedation and 45% of subjects in the highest dose group would require rescue medication use for sedation. Thus, with 14 subjects in the low and high dose groups, there would be 72% power to detect the difference, assuming a 1-sided, $\alpha$=0.05, test for two proportions.

Inclusion Criteria:
(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 ranges2 at screening:
    a. Preterm neonates ≥ 28 weeks through < 36 weeks, gestational age; this constituted treatment age group I.
    b. Term neonates born at ≥ 36 weeks through ≤ 44 weeks gestational age; this constituted treatment age group II.
(4) Weight: subject's weight at the time of enrollment had to be > 1000 g.
(5) Subject's parent(s) or legal guardian(s) voluntarily signed and dated the informed consent document approved by the IRB/IEC.

Exclusion Criteria:
(1) Neonate subjects with neurological conditions that prohibited an evaluation of sedation such as:
    a. Diminished consciousness from increased intracranial pressure.
    b. 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.

2 Gestation age (in weeks) was calculated as follows: the time elapsed between the first day of the last menstrual period and the day of enrollment.

c. 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 subject had a pacemaker or pacing wires were in situ.
   a. In subjects status-post (s/p) cardiopulmonary bypass (CPB) managed without pacing wires in situ, the subject could not have been suspected to be in second or third degree heart block at the time of DEX administration.
(3) Heart rate < 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 alanine aminotransferase (ALT) levels > 115 U/L.

Endpoints and Analyses

Analysis Populations:

- Enrolled Subjects - subjects who signed the inform consent and did not screen fail.
- Intent-to-Treat (ITT) Population - subjects that met all inclusion criteria and no exclusion criteria
- Safety Evaluable (SE) Population - population that received any study drug. Used in all safety reporting and analyses.
- Efficacy Evaluable (EE) Population- received study drug for at least 6 hours. The primary population for efficacy analysis.
- Pharmacokinetic (PK) Population - received a minimum of 6 hours of DEX infusion with adequate PK samples to estimate primary parameters. The primary analysis population for the PK analyses.

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

*Primary Endpoint Analysis*
The primary efficacy variable was summarized for each dose level with descriptive statistics (N, mean, SD, median, min, Q1, Q3, and max). The difference between age groups will be assessed as risk differences for 2x2 tables with 95% confidence interval with and without a continuity correction using PROC FREQ in SAS.

Secondary Endpoints:

- Incidence of rescue medication use for analgesia during DEX infusion
- 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 (HR, SBP, DBP, MAP, RR) and oxygenation (SpO2) measures during DEX infusion
- Time spent with a total N-PASS score >3 and ≤3 during DEX infusion
- Time to extubation in DEX-exposed subjects

Changes in Protocol or Planned Analyses

The main reasons for Amendment 1 dated 14 October 2010 were as follows:

(1) Clarification of Section 6.1, Overall Study Design and Plan, for clarity of dosing levels, primary and secondary variables, and assessments.
(2) Clarification of Inclusion Criterion #3 (regarding the calculation of gestational age) and exclusion criteria #2 (note added regarding s/p CPB subjects) and #6 (to eliminate the need for urine drug screen of the mother).
(3) Clarification that prior therapy was allowed.
(4) Clarification of when rescue modification was needed, which rescue medications were acceptable, and when N-PASS was performed in relation to rescue medications.
(5) The study activity table was modified: 24-hour physical examination was added, footnote “e” baseline ECG clarified, and the urine drug screen test was deleted.
(6) Addition of a 24-hour post-DEX infusion physical examination.
(7) Gestational age calculation was clarified.
(8) Clarification of the time 12-lead ECGs were obtained and to delete clinically significant abnormality from the study exclusion.
(9) Modification of the clinical laboratory table to distinguish between screening subjects and CPB subjects and to delete the urine drug screen test.
(10) Deletion of the urine drug screen.
(11) Clarification of the different PK sampling times for different age groups.
(12) Clarification of collection times for the N-PASS.
(13) Clarification of safety variable analysis.
(14) Clarification of the primary efficacy endpoints.
(15) Clarification of the preparation of study medication section.
(16) Modification of the AE section to describe Investigator responsibility for awareness of clinically meaningful cardiopulmonary AEs.
(17) Clarification of the AE collection period.
(18) The SE Population was defined.
(19) Clarification of the baseline value definition.

(20) Clarification of the reporting strategy for subjects with multiple AEs.
(21) Clarification that vital signs were that were to be included in the safety assessments.
(22) Clarification of the statistical tests to be used for pairwise comparison in the primary efficacy analysis.
(23) Clarification of how extubated subjects would be analyzed.
(24) Addition of dosing tables and title change ("Recommended Loading and Maintenance Doses") in Appendix D.
(25) Modification of Appendix F (Expected AEs and SAEs Following Cardiothoracic Surgery in Neonates) to remove #5 and #6 under cardiovascular.
(26) Administrative changes to the title page.

Changes in planned analysis were the following:

1. A secondary efficacy endpoint was added for N-PASS data ≤ 3 during DEX infusion.
2. Derived variables were added to listings pertaining to:
    a. Time spent with an N-PASS total score ≤ 3 during DEX infusion.
    b. Time spent with an N-PASS total score > 3 during DEX infusion.
    c. Total amount and the weight adjusted total amount (per kg) of rescue medication for sedation and analgesia during DEX infusion.

**Medical Reviewer Comments:**
The Applicant provided several reasons for the dose selections in DEX-09-08, which were considerably lower than doses administered to subjects >44 weeks of age. The Applicant's primary reason for selecting these doses was a case report of bradycardia in a 5-week old infant who was also taking digoxin, but received DEX at an infusion rate of 0.44 mcg/kg/hour. The Applicant also reasoned that the youngest pediatric subjects should require less DEX because of their immature blood-brain barrier and should receive less DEX because of their heart rate dependent cardiac output.

The patient population selected for DEX-09-08 left out one group of neonates. Preterm infants aged 28 to <36 weeks were eligible for DEX-09-08, as were term infants aged 36 to 44 weeks at time of enrollment. However, subjects who were born prematurely but aged 36 to 44 weeks were not eligible for enrollment in the trial. Their exclusion likely excluded a significant portion of subjects in the 36 to 44 week age range, that might, because of prematurity and a prolonged ICU course, tend to be a more medically complicated and pharmaceutically tolerant patient population. Conversely, term subjects aged 36 to 44 weeks who were enrolled might reflect a largely post-operative surgical subject population, and not fully represent the population of subjects age 36 – 44 weeks that might be candidates for DEX sedation.

**Study 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

Objective

The primary objective of this study was to characterize the safety and efficacy of DEX administered as an intravenous (IV) loading dose followed by a continuous IV infusion in preterm subjects, ages ≥ 28 weeks through < 36 weeks gestational age.

Design

This was a Phase II/III open-label, multicenter, safety, efficacy, and PK study of DEX in preterm subjects. The study population consisted of initially intubated and mechanically ventilated male and female neonates, ages ≥ 28 weeks to < 36 weeks gestational age, who required sedation in an intensive care setting for a minimum of six hours. A total of six subjects, admitted to the Neonatal Intensive Care Unit (NICU), PICU, or Cardiac Intensive Care Unit (CICU), were enrolled at three investigative sites. All subjects received the same treatment.

**Table 8 Schematic Diagram of Study DEX-11-06 Design**

| DEX Infusion Period | | Post-Infusion Period (24 hours) | Up to Discharge or Study Day 7 |
|---|---|---|---|
| DEX load 0.2 mcg/kg over 10 or 20 min | DEX maintenance 0.2 mcg/kg/hr (at least 6 and up to 24 hours) | | |
| | N-PASS with rescue sedation (MDZ) or rescue analgesia (morphine or fentanyl) | | |
| | Efficacy and safety measures | Efficacy and safety measures | Safety Monitoring |

DEX=dexmedetomidine; N-PASS =Neonatal Pain, Agitation, and Sedation Scale; MDZ=midazolam.

Treatments and Interventions

Test Treatments:
DEX was administered as a 2-stage infusion:

(1) A 10- or 20-minute loading dose infusion of DEX 0.2 mcg/kg.

(2) A continuous fixed maintenance dose infusion of DEX 0.2 mcg/kg/hour for a minimum of six and maximum of 24 hours post-operatively.

Rescue Medications:
Certain rescue medications were administered as need for sedation and pain following the same procedure as in Study-DEX-09-08, the previous trial outlined above.

Concomitant Medications:
Prohibited medications were the same as in Study-DEX-09-08, outlined above.

Populations

Inclusion Criteria:
(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) Age at screening: ≥ 28 weeks through < 36 weeks, gestational age[3]
(3) Weight: subject's weight at the time of enrollment had to be > 1000 g.
(4) Subject's parent(s) or legal guardian(s) voluntarily signed and dated the informed consent document approved by the IRB/IEC.

Exclusion Criteria:
(1) Neonate subjects with neurological conditions that prohibited an evaluation of sedation such as:
    a. Diminished consciousness from increased intracranial pressure.
    b. 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.
    c. 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 subject had a pacemaker or pacing wires were in situ.
    a. In subjects status-post (s/p) cardiopulmonary bypass (CPB) managed without pacing wires in situ, the subject could not have been suspected to be in second or third degree heart block at the time of DEX administration.
(3) Heart rate < 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.

[3] Gestational age (in weeks) was calculated as follows: the time elapsed between the first day of the last menstrual period and the day of enrollment.

(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 alanine aminotransferase (ALT) levels > 115 U/L.

Endpoints and Analyses

Primary Endpoint:
The primary efficacy endpoint for the study was the frequency of subjects requiring any rescue medication for sedation during DEX infusion.

Secondary Endpoints:
- Incidence of rescue medication (fentanyl or morphine) for analgesia during DEX infusion
- Amount of rescue medication (MDZ) for sedation during DEX infusion
- Amount of rescue medication for analgesia during DEX infusion
- Change from baseline in vital signs (HR, BP, MAP), respiratory rate (RR) and oxygenation (SpO2) measures during DEX infusion
- Time spent with a total N-PASS score >3 during DEX infusion
- Time from DEX administration to extubation (for subjects extubated while on DEX)

Changes in Protocol of Planned Analyses

Protocol Amendments:
Changes to the protocol were made once during the study. A new amended clinical study protocol was compiled on 19 Dec 2011.

*Amended Clinical Study Protocol (19 Dec 2011)*
Most of the changes were only clarifications that did not affect the conduct of the study. The Applicant's summary of changes follows:
1. Section 8.3.2.1 Preparation of Study Medications was modified to clarify a typographical error that the loading dose concentration of 0.05 mcg/mL solution should be 0.5 mcg/mL solution.
2. Sections 1.0 Protocol Synopsis, 2.0 Study Activities, 4.0 Introduction and Background, 5.1.1 Primary Objective, 5.1.2 Secondary Objective, 5.2.2 Secondary efficacy endpoints, 6.1 Overall Study Design and Plan, Figure 1 Study

Schematic, 6.2.2 Baseline, 6.2.3. DEX Administration, 6.2.4 Post-Study DEX Administration, 7.1.1 Inclusion Criteria, 8.1.4 Concomitant Therapy, 8.1.5 Rescue Therapy, 8.4.1 discussion of Study Design and Choice of Treatment Groups, 8.4.2 Appropriateness of Measurements, 8.43. Selection of Doses in the Study, 9.1.3
Pharmacokinetic Sampling, 9.11 Laboratory Evaluations, 9.15.1 Pharmacokinetic Variables, 12.1 Statistical And Analytical Plans, 12.1.1.3 Pharmacokinetic (PK) Population, 12.1.2. Demographic and Baseline Characteristics, and 12.1.6. Pharmacokinetic Analysis have been modified to remove references to pharmacokinetic sampling and analysis. FDA has given Hospira an indication that the pharmacokinetic results already collected for the neonate population are sufficient to characterize pharmacokinetics of dexmedetomidine in this population. Therefore, collection of blood samples for the determination of pharmacokinetics in this study is no longer justified.

3. Section 8.4.3 - Selection of Doses in the Study was modified to add verbiage to provide a clearer understanding for the selection of doses.

*Supportive (PK/PD) Studies*

**CHOP Study**

The Pharmacokinetics, Pharmacogenetics, and Pharmacodynamics of Dexmedetomidine in Infants Postoperative from Cardiac Surgery

Objectives

The primary objectives of this study were defined in the protocol as the following:

- To define the pharmacokinetics (PK) of increasing doses of dexmedetomidine administered as an intravenous (IV) bolus followed by continuous IV infusion (CIVI) in infants who were post-operative from cardiac surgery

- To describe the pharmacodynamic (PD) effects of dexmedetomidine in infants (age: 1 month to 2 years) who were post-operative surgical patients during the 24-hour period prior to, and during, extubation

The secondary objectives for this study are listed below. There were some differences between objectives named in the protocol and the study report, and those objectives not included in both documents are identified as such:

- To obtain correlation data on the relationship between level of sedation and dexmedetomidine plasma drug concentration in infants post-operative from cardiac surgery.

- To evaluate safety in the 1 month to 2 year old patient population (per study report).

- To explore the utility of a non-invasive measurement of sedation, the BIS monitor, in infants postoperative from cardiac surgery (per original protocol).

- To obtain preliminary data on the relationship between level of sedation and dexmedetomidine plasma drug concentration in infants postoperative from

- cardiac surgery (per original protocol).

- To obtain preliminary data on the relationship between polymorphisms in CYP2A6, specific UGT isoforms, and alpha2-adrenoreceptors to drug response (efficacy or toxicity) in infants postoperative from cardiac surgery receiving dexmedetomidine (per original protocol).

Design

This was a Phase I, open-label, single center, dose escalation study evaluating the PK and PD of DEX in pediatric subjects after cardiac surgery. Subjects were screened preoperatively as per the Schedule of Assessments (**Error! Reference source not found.**), and considered eligible if they were 1 month to 2 years old, requiring mechanical ventilation postoperatively, and met other enrollment criteria. Three bolus and infusion dose combinations of dexmedetomidine were studied and twelve patients were studied at each dose level.

**Table 9 CHOP Schedule of Assessments**

| Evaluation | Screening | Pre-op Pre-dose | Intra-op | Post-op Pre-dose | Post-dose | Post Study Drug |
|---|---|---|---|---|---|---|
| Medical History | X | | | | | |
| Physical Examination | X | | | | | |
| Inclusion/Exclusion | X | | | | | |
| Demographics | X | | | | | |
| Birth History | X | | | | | |
| Echocardiogram History | X | | | | | |
| Cardiopulmonary | | | X | | | |
| Clinical Laboratory | X | | | X | | X |
| Vital Signs | X | | | X | | X |
| BIS Monitor | | | | X | X | |
| UMSS | | | | X | X | |
| ECG | X | | | X | | X |
| Informed Consent | X | | | | | |
| Enrollment | | X | | | | |
| Pharmacokinetic[a] | | | | | X | X |
| Concomitant Med | X | X | X | X | X | |
| Adverse Events | X | X | X | X | X | X |

BIS=Bispectral Index Scale; ECG=electrocardiogram; EOI=end of infusion; op=operative; UMSS=University of Michigan Sedation Scale.

[a] Plasma pharmacokinetic samples were collected prior to the bolus dose, in close proximity to 0.5, 1, 2, 4 to 6 hours after the start of the infusion, 15 to 30 minutes prior to the end of the infusion (EOI), and 0.25, 0.5, 1, 2, 4, 8, 12, and 15 to 18 hours after the EOI. A total of 14 mL was collected for pharmacokinetics.

As this was a dose-escalation study, an algorithm was in place for dose advancing the dose as follows:

(1) If more than two patients at a dose level experienced a dose-limiting toxicity (DLT) that was possibly, probably, or definitely related to study drug, the

maximum tolerated dose (MTD) had been exceeded and no additional patients would be studied at that dose level.
(2) If the MTD was exceeded with the first dose group, (see **Error! Reference source not found.**, Dose Level 1), the next cohort would receive a lower dose, specifically 0.25 mcg/kg bolus followed by 0.14 mcg/kg/hour infusion.
(3) If the MTD was exceeded at Dose Level 2 or 3, the protocol would have been stopped.
(4) Any single life-threatening event possibly or probably attributed to the study drug would result in study suspension.
(5) The decision to escalate the dose was based on the review of safety and PK data for all patients in the previous cohort; if the median clearance was less than 70% of that reported in adults (35 L/hour), the study would be stopped.

Treatments and Interventions

Test Treament:
Treatment of study subjects are outlined as follows. Eligible patients received 4 mg/kg pentobarbital premedication by mouth, and followed by intraoperative fentanyl 20 mcg/kg and pancuronium 0.4 mg/kg in divided doses. The investigator the administered the study drug loading dose over ten minutes followed by a maintenance intravenous infusion. Subjects received one of three escalating study drug regimens, as shown in Table 10below. Subjects received the study drug during the extubation process and were extubated upon meeting respiratory criteria.

**Table 10 CHOP Inter-Patient DEX Dose Escalation**

Concomitant Mediations:
Concomitant medications were restricted. When the DEX infusion provided inadequate sedation, additional sedation or analgesia was administered to in the form of fentanyl (0.25 – 1 mcg/kg/dose), morphine (10 – 100 mcg/kg/dose), and midazolam (10 – 100 mcg/kg/dose). Additionally, patients were not allowed to receive continuous infusion of muscle relaxants.

Populations

Sample Size:
Sample size was determined by CHOP, and based upon determining the PK profile of DEX. A difference for AUC and $C_{ss}$ for three dosing groups with alpha 0.05 and power

eighty percent would be detected with a total of thirty-six subjects given an inter-patient variability of 50% for steady state concentration.

Inclusion Criteria:

(1) Age: Patients must be ≥ 1 month and ≤ 24 months.
(2) Diagnosis: Post-operative from cardiac surgery with tracheal intubation/mechanical ventilation in the immediate post-operative period and planned tracheal extubation within 24 hours post-operatively.
(3) Adequate Renal Function Defined As serum creatinine ≤ 0.6 mg/dL for subjects ≤ 12 months and serum creatinine ≤ 1.0 mg/dL for subjects > 12 months.
(4) Adequate Liver Function Defined As Total bilirubin ≤ 1.5 mg/dL and SGPT (ALT) ≤ 165 U/L for subjects ≤ 12 months and ≤ 90 U/L for subjects > 12 months.
(5) Isolated heart surgery.
(6) Informed Consent: All parents or legal guardians must sign a written informed consent.

Exclusion Criteria:

(1) Concomitant Medications
   a. Investigational Drugs: Patients who have received another investigational drug within the past 30 days.
   b. Muscle relaxation: Receiving continuous infusions of muscle relaxants in the postoperative setting.
(2) Infection: Patients who have a positive blood culture without a subsequent negative culture or other evidence of ongoing serious infection.
(3) Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.
(4) Patients who show signs or symptoms of elevated intracranial pressure. These may include, but are not limited to, Cushing's triad (hypertension, bradycardia, and bradypnea), lethargy, bulging fontanelle, and seizures.
(5) Post-operative hypotension based on age
   a. 1 month - 2 months: systolic ≤ 45, diastolic ≤ 25, or mean arterial pressure ≤ 35 mm Hg.
   b. 2 months - 6 months: systolic ≤ 55, diastolic ≤ 35, or mean arterial pressure ≤ 45 mm Hg.
   c. 6 months - 24 months: systolic ≤ 65, diastolic ≤ 45, or mean arterial pressure ≤ 55 mm Hg.
(6) Pre-existing bradycardia based on age
   a. month- 2 months: heart rate ≤ 90.
   b. 2 months - 12 months: heart rate ≤ 80
   c. 12 months - 24 months: heart rate ≤ 70.
(7) Heart block.
(8) Weight < 5 kg.
(9) Patients who, in the opinion of the investigator, are not appropriate candidates for an investigational drug study.

Endpoints and Analyses

Endpoints:
Primary and secondary endpoints were not defined in the protocol. However, given the primary objective of defining DEX pharmacokinetics and pharmacodynamics, the endpoints can be determined from the study protocol in part 13.1, Pharmacokinetic Analyses, and part 10.4.1, Pharmacodynamic Assessments,.

Pharmocokinetics of DEX, a primary objective, was assessed through the following parameters:

- AUC (area under the plasma concentration-time curve)
- $t_{1/2}$ (terminal half-life)
- Css (steady state concentration)
- Cl (plasma clearance)
- Vd (volume of distribution)

Pharmacodynamic effects, a primary objective, was assessed through the following variables which were monitored hourly until 24 hours after study drug discontinuation:

- Heart rate (beats/min)
- Mean arterial pressure (mm Hg)
- Systolic blood pressure (mm Hg)
- cardiac rhythm
- Respiratory rate (breaths/min)
- Oxygen saturations

Changes in Protocol or Planned Analyses

Protocol Changes:
The protocol was amended four times during the conduct of the study and once prior to study initiation. Only the final protocol was presented in the submission. The four amendments, as taken verbatim from the Applicant, follow:

*Amendment 1 (19 July 2004)*

1. Section 6.1 – Modified to limit inclusion criteria to isolated heart surgery.
2. Section 7.1 – Added to provide for standardization of intraoperative anesthetic.
3. Section 13.2 – Modified to further explain the correlative study analyses.

*Amendment 2 (12 Oct 2004)*
Minor modifications made to:

1. Section 7.3.1 & 10.2.2 – Change to read, “In close proximity to 72 hours...”

2. Section 10.4.2 – Statement included for BIS sensor to be removed from the patient's head after infusion is discontinued when patient is deemed awake.
3. Section 10.4.4 – Statement change to read, "The infusion may be continued at the discretion of the clinical care team…."
4. Section 13.1 – Statement change to read, "Data from all fully evaluable patients…. At least 2 hours…" and "The following pharmacokinetic parameters… using the NONMEM® statistical algorithm."

*Amendment 3 (22 Oct 2004)*
Section 7.5 - Modifications made to provide clarification of dose limiting toxicity (DLT).

*Amendment 4 (13 July 2005)*
Preliminary analysis from first dosed patients indicated the PK sampling schedule should be adjusted to provide better representation of the PK profile of DEX in that patient population. The number of PK samples did not change.

Changes in Statistical Analysis:
The Statistical Analysis Plan (SAP) in the submission was established by the Applicant after obtaining the data from CHOP, and the Applicant reported the following differences between the CHOP's planned analysis and those in the Applicant's SAP:

1. DLT Definition: The protocol in sections 7.5.1 and 7.5.2 includes bradycardia and hypotension defined by age, clinically relevant oversedation, and SAEs as DLTs. The SAP includes only bradycardia defined by age, hypotension defined by age, and bradypnea defined by respiratory rate.
2. ECGs: The protocol states that ECGs were obtained pre- and post-treatment and compared for evidence of new ischemia. However, the Applicant reported that "ECG charts and QT intervals were not available and there was no plan to analyze the ECG data."
3. Pharmacogenomics: The protocol referenced collection of plasma samples for pharmacogenomic testing; however, no samples were collected for pharmacogenomic testing or analysis.

**Study DEX-08-01**

A Phase 2, Open-Label, Multicenter, Escalating Dose Study to Determine the Pharmacokinetic and Pharmacodynamic Profile of Dexmedetomidine in Pediatric Subjects Ages ≥2 through <17 Years Old

Objectives

The objective of this study was to characterize the PK and PD profile of DEX administered as an IV loading dose followed by a continuous IV infusion in pediatric subjects ages ≥ 2 through < 17 years old.

Design

This was a Phase 2, open-label, multicenter, escalating dose study evaluating the PK and PD of DEX in pediatric subjects. The study population consisted of initially intubated and mechanically ventilated pediatric subjects, ages ≥ 2 through < 17 years old, who required sedation in an intensive care setting for a minimum of six hours but not to exceed 24 hours. Subjects with ages ≥ 2 through < 6 years old were enrolled in Group I and those with ages ≥ 6 through < 17 years old were enrolled in Group II. Within each group, there were four escalating dosing levels. Following completion of the loading dose, the continuous maintenance infusion began. After the subjects completed the DEX maintenance infusion for a minimum of six hours but not to exceed 24 hours, the maintenance infusion was discontinued and the post-infusion procedures began and continued for 24 hours. The DEX infusion rate was not titrated during this trial.

Treatments and Interventions

Test Treatment:
The dosing regimen for this study is found in Table 11.

**Table 11 DEX-08-01 Dosing Regimen**

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

Source: Appendix 16.1.1.
Abbreviations: DEX=dexmedetomidine; DSMB= Drug Safety Monitoring Board; FLACC= Faces, Legs, Activity, Cry, and Consolability; MDZ=midazolam; RASS=Richmond Agitation Sedation Scale; RSS=Ramsay Sedation Scale.
a. The level of sedation (RSS and RASS with rescue MDZ) and the level of pain (FLACC scale with fentanyl rescue) were documented at the beginning of the loading, 5 and 10 minutes after the load, hourly during the maintenance infusion period and within 5 minutes after administration of rescue medication.
b. DEX infusion started after discontinuation of other sedative and analgesic infusions when the subject was in a RSS range of 2, 3, or 4. Subjects could be extubated at any time following the start of the loading dose.
c. DSMB gave approval before subjects enrolled into the next level.

The Sponsor based the lowest dose, 0.25 mcg/kg loading over 10 minutes followed by 0.2 mcg/kg/hr maintenance, on the reported minimum effective dose of DEX for sedation in mechanically ventilated patients. The highest dose, 1.0 mcg/kg load followed by 2.0 mcg/kg maintenance was, according to the Sponsor, based on reports

of higher doses of DEX required for sedation of children and increased tolerance of higher doses in children without adverse effects.

At any time clinically indicated (e.g., subject discomfort despite maximum dose of rescue), at the discretion of the investigator or designee, the subject may have been converted to alternative sedative or analgesic therapy.

If more than two subjects at a dose level experienced a DLT that was probably or definitely attributable to study drug, the maximum tolerated dose (MTD) for the drug was exceeded and no additional subjects were studied at that dose level. If the MTD had not been exceeded at the first dose level, then the subsequent cohort of subjects was treated at a 0.50 mcg/kg loading dose and a 0.4 mcg/kg/hr infusion, and so on until a MTD dose level was reached or Dose Level 4 was completely enrolled. If the MTD had been exceeded at the third or fourth dose levels, enrollment to the protocol was stopped.

Concomitant Medications:
Use of the following drugs was prohibited during the study drug infusion period:

- Sedatives and analgesics other than DEX, MDZ, or fentanyl.
  - Acetaminophen was permitted only as an anti-pyretic during DEX infusion.
- Any continuous infusion of neuromuscular blocking agents.
- Any drugs contraindicated with the use of DEX, MDZ, or fentanyl.
- Agents to induce sleep (eg, triazolam, diphenhydramine).
- Epidural or spinal anesthetic or analgesic agents during the DEX infusion period.
- Subjects who remained intubated or were re-intubated during the post-infusion period or required sedation for other reasons during the post-infusion period were treated according to standard of care at the study site. This care did not include DEX until all post-infusion PK samples were obtained.
- None of the alpha-2 agonists/antagonists listed in Appendix C of the protocol (Appendix 16.1.1) could be used within 48 hours prior to the study or during the Study Drug Infusion Period.

Rescue Medications:
MDZ or fentanyl were administered as needed for sedation and pain, respectively, during study drug administration based on results of the sedation (RSS and RASS) and pain (FLACC) scales.

*Midazolam*
A subject who was not adequately sedated (based on an RSS score < 2 or clinical judgment) was administered MDZ. Rescue MDZ was given according to the label:

- 6 months to 5 years old: 0.05 to 0.1 mg/kg
- 6 to 12 years old: 0.025 to 0.05 mg/kg
- Older than 12 years: 1 mg

RSS, RASS and FLACC scores were obtained prior to administering MDZ and within 5 minutes after administration of MDZ. The package insert recommended 2 to 3 minutes between MDZ doses; however, this was left to the discretion of the investigator. The date, time and exact dose of MDZ, as well as the reason for use, were recorded on the CRF.

*Fentanyl*
Rescue fentanyl (0.25 to 1 mcg/kg IV), was given if pain was present. FLACC scores were documented before fentanyl administration, and for every dose of fentanyl, a justification fitting into one of the following categories was used and recorded on the CRF:

- FLACC Score >4
- Verbal communication was not possible – presence of pain based on the investigator's judgment.

Populations

Sample Size:
The sample size of this study was based on the number of subjects required in a typical PK study, not based on statistical power calculations.

Table 12 shows the minimum number of subjects that the Applicant required for each dose level within each age group. According to the Applicant, the sample size was based on input from the FDA contained in the Written Request. Subjects were to be distributed approximately equally between sexes at each dose level.

**Table 12 DEX-08-01 Subjects per Dosing Level**

| Dosing Levels | Group I (Age: ≥2 years to <6 years) | Group II (Age: ≥6 years to <17 years) |
|---|---|---|
| Dose Level 1 | N = 6 | N= 8 |
| Dose Level 2 | N = 6 | N= 8 |
| Dose Level 3 | N = 6 | N= 8 |
| Dose Level 4 | N = 6 | N= 8 |
| Total | N = 24 | N= 32 |

Source: Appendix 16 1 9

Inclusion Criteria:

(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) Age: Subjects must have fit into 1 of the following age ranges at screening:

a. ≥ 2 years old through < 6 years old.
b. ≥ 6 years old through < 17 years old.

(3) If female, subject was non-lactating and was either:
   a. Not of childbearing potential, defined as pre-menarche, or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy or hysterectomy.
   b. Of childbearing potential, not pregnant based on urine pregnancy test at baseline.
(4) Subject's parents(s) or legal guardian(s) had voluntarily signed and dated the informed consent document approved by the IRB. Assent was obtained where age-appropriate and according to state regulations.

Exclusion Criteria (at Screening except as noted below):

(1) Pediatric subjects with neurological conditions that prohibit an evaluation of sedation such as:
   a. Diminished consciousness from increased intracranial pressure.
   b. Extensive brain surgery (surgery requiring intracranial pressure monitor);
   c. Diminished cognitive function per PI's discretion,
   d. Subjects with immobility from neuromuscular disease or continuous infusion of neuromuscular blocking agents.
(2) Weight <10 kg.
(3) Subjects with second degree or third degree heart block unless subject had a pacemaker or pacing wires.
(4) Hepatic impairment defined as SGPT (serum glutamic pyruvic transaminase) / ALT (alanine aminotransferase) > 100 U/L.
(5) Hypotension based on repeat assessments prior to starting study drug:
   a. Age ≥2 years old through ≤12 years old: systolic blood pressure (SBP) <80 mmHg
   b. Age >12 years old through <17 years old: SBP <90 mmHg
(6) Pre-existing bradycardia prior to starting study drug defined as:
   a. Age ≥2 years old through ≤6 years old: ≤70 beats per minute (bpm).
   b. Age >6 years old through ≤12 years old: ≤60 bpm.
   c. Age >12 years old through ≤16 years old: ≤50 bpm.
(7) Acute thermal burns involving more than 15% total body surface area.
(8) Subject who had a known allergy to DEX, MDZ, or fentanyl.
(9) Subjects with a life expectancy that was <72 hours.
(10) Subjects who were expected to have hemodialysis (continuous hemofiltration) or peritoneal dialysis within 48 hours.
(11) Subjects who had been treated with α-2 agonists/antagonists within 2 weeks (see Appendix C of the study protocol [Appendix 16.1.1]).
(12) Subjects with a spinal cord injury above T5.
(13) Subjects who had received another investigational drug within the past 30 days.
(14) Subjects on nicotine replacement therapy.
(15) Subjects who, in the opinion of the investigator, were not able to comply with the safety monitoring requirements of this clinical study.

Endpoints and Analyses

Primary Endpoint:
The primary evaluation was the assessment of DEX PK. The PK parameters estimated included:

- AUC (area under the plasma concentration-time curve)
- Cmax (observed peak plasma concentration)
- Css (steady state concentration)
- CL (plasma clearance)
- Vss (volume of steady state distribution)
- t1/2 (terminal half-life)

Secondary Endpoints:

- Level of sedation according to the RSS as the primary sedation scale and the RASS as exploratory.
- Pain score according to the Face, Legs, Activity, Cry, and Consolability (FLACC) test.
- Time to first use of rescue midazolam (MDZ) for sedation
- Total amount of rescue MDZ
- Total amount of rescue fentanyl
- Vital signs including heart rate (HR), mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), and oxygen saturation by pulse oximetry (SpO2)
- The top 10 adverse events (AEs) that occurred most frequently among all subjects
- Time to successful extubation (defined as an extubation that did not require another reintubation within 12 hours).

Changes in Protocol or Planned Analyses

Protocol Amendments:
The protocol was amended once prior to study initiation and once shortly after study initiation.

*Amendment 1 (9 May 2008)*
The primary purpose of this amendment was to:

1. Modify Section 6.3.1.1.15 to decrease the number of blood draws for the PK sampling procedures.
2. Add an exclusion criterion to include screening albumin levels.

3. Clarify the exclusion criteria for hypotension and pre-existing bradycardia prior to starting study drug.
4. Clarify times for ECG and Laboratory Evaluations.
5. Clarify times for use of the RSS, RASS, and FLACC scales.
6. Clarify respiratory depression dose limiting toxicity.
7. Modify section on liver function.
8. Clarify the Discontinuation of Individual Subjects (Section 6.4.1).
9. Add an appendix to include the Elements of Informed Consent (Appendix H).

*Amendment 2 (12 Dec 2008)*
The primary purpose of this amendment was to:

1. Update Review and Approval page.
2. Modify Section 6.1 to change the language of re-introducing DEX post- DEX infusion to be consistent with Section 6.2.3.2.
3. Modify Table 2 to delete input/output fluid collection from post- DEX administration period. This change is consistent with the current language in Section 6.3.1.1.13.
4. Modify Section 6.2.2 to delete the exclusion criterion for screening albumin levels.
5. Modify Section 6.2.3.1 to change the length of time for recording subject prior medication usage from 14 days to 48 hours prior to the start of study drug infusion.
6. Modify Section 6.3.1 to delete input/output collection from post- DEX administration in the flow chart;
7. Modify Section 8.5 to clarify the SAE reporting and to correct the name of the SAE reporting unit;
8. Modify Section 9.0 to include contact information for the study Clinical Project Manager;
9. Modify Appendix C to change the length of time for prior use of alpha-2 agonists/antagonist.

Changes in Statistical Analysis:

1. Per the SAP addendum, the following text was added to Section 7.5 Safety Analysis of the SAP clarifying that safety analysis was to be done on a subset of subjects that were at high risk to undergo CPB:

   *Safety analysis in terms of AEs, TEAEs, hemodynamic variables and outcomes will be evaluated in subjects that underwent CPB and compared to subject that did not undergo CPB.*

2. CPB will be determined by review of individual cases for a) indication of intubation and b) pre-existing medical conditions (especially cardiac, such as presence of a murmur) prior to the start of study drug to determine subjects that

were at high likelihood to have undergone CPB. This review will be conducted by the medical monitor.

3. There was one change to the planned analyses that was not included in the SAP Addendum: The original SAP stated that lab shift tables based on normal and abnormal levels would be produced, but they were not.

**Medical Reviewer Comments**:
In compliance with the PWR, this was the first study initiated by the Applicant, involving PK/PD evaluation in older pediatric subjects. It is notable for its highest dose group that received a maintenance dose of 2 mcg/kg/hour, which was more than twice the dose administered to the high dose groups in the other trials.

**Study 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

Objectives

Primary Objectives:

- To define the pharmacokinetic (PK) profile of DEX administered as an intravenous loading dose followed by a continuous intravenous infusion in pediatric subjects 12 months through < 24 months of age.
- To define the pharmacodynamic (PD) profile of DEX administered as an intravenous loading dose followed by a continuous intravenous infusion in pediatric subjects 12 months through < 24 months of age.

Secondary Objective:

- To evaluate the safety of DEX in subjects 12 months through < 24 months of age.

Design

DEX-11-01 is a Phase II, randomized, open-label, single-center, study evaluating the PK and PD of DEX in pediatric subjects administered DEX as a two-stage infusion across two dose levels. The study population consisted of intubated and mechanically ventilated pediatric subjects aged 12 months to < 24 months, who required sedation in an intensive care setting for a minimum of 6 hours but not more than 24 hours.

Subjects were screened for eligibility as per Table 13 below.

**Table 13 DEX-11-01 Schedule of Events**

| Procedure | Screening (72 Hours Before Study Drug Administration) | DEX Administration | Post-DEX Administration |
|---|---|---|---|
| Informed Consent | X | | |
| Demographics | X | | |
| Medical History | X | | |
| Physical Exam | X | | X |
| Inclusion/Exclusion | X | | |
| Reason for Intubation | X | | |
| Enrollment | X | | |
| Heart Rate[1] | X | X | X |
| Blood Pressure[1,2] | X | X | X |
| Respiratory Rate[1,3] | X | X | X |
| Oxygen Saturation (%)[1] | X | X | X |
| ECG[4] | X | X | X |
| Body Temperature (Tympanic)[1] | X | X | X |
| Body Weight | X | | |
| Laboratory Evaluation (chemistry, hematology & urinalysis)[5] | X | X | X |
| Input/Output Fluid Volumes | | X | X |
| Pharmacokinetic Sampling[6] | | X | X |
| FLACC[7] | X | X | X |
| Fentanyl Use[8] | | X | X |
| UMSS[9] | | X | X |
| Midazolam Use[10] | | X | X |
| Prior Medication | X | | |
| Concomitant Medication | | X | X |
| Adverse Events | X | X | X |

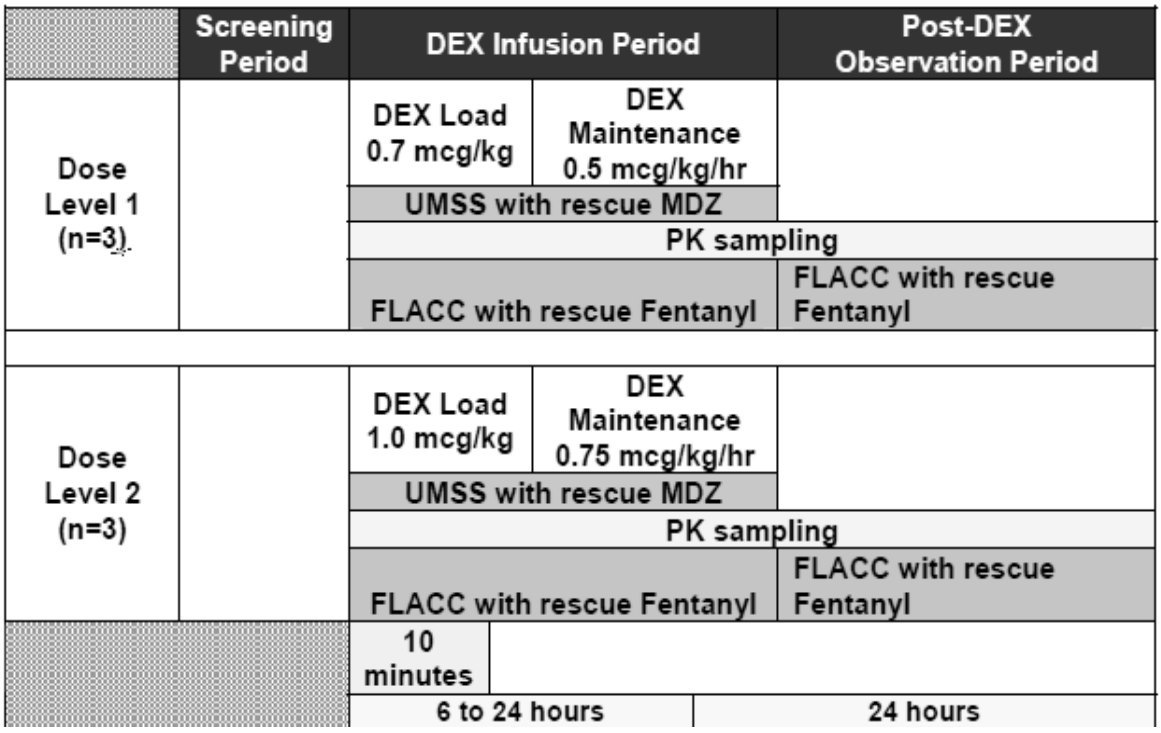
1. Recorded prior to, at 5 and 10 minutes during the load, hourly during the maintenance infusion period and up to 5 minutes before PK sampling times. After discontinuation of maintenance infusion recorded every 15 minutes for the 1st hour, every 30 minutes for 2 hours, every hour for 3 hours and each hour until the last PK sample has been obtained.
2. Either non-invasive or continuous arterial pressure monitoring.
3. If subjects are mechanically ventilated, both the subjects' respiratory rate and ventilator rate are recorded
4. ECGs will be collected at 3 timepoints: At Predose, between 4-6 hour after start of maintenance infusion, and 10 hours after end of maintenance infusion.
5. Laboratory evaluations will be drawn at 3 timepoints: Predose, between 4-6 hour after start of maintenance infusion, and 10 hours after end of maintenance infusion. To avoid extra blood draws, laboratory evaluations should be drawn simultaneously with one of the scheduled PK samples
6. PK samples to be taken at the following times: 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.
7 Obtain FLACC scores according to the following schedule:
• Immediately prior to the loading dose
• Hourly during the maintenance infusion
8. Obtain FLACC 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 is titrated, collect within 5 minutes prior to and within 5 minutes following titration.

9. Obtain UMSS scores according to the schedule below:
• Just prior to loading dose, and then at 5 and 10 minutes during loading dose.
• At the start of maintenance of infusion, 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.
10.Obtain UMSS immediately before and within 5 minutes after any midazolam rescue during DEX infusion period.

Treatments and Interventions

Test Treatment:
Treatments for study subjects are outlined as follows. After enrollment, subjects were randomized to receive one of 2 dose levels: Dose Level 1 consisted of a 0.7 mcg/kg loading dose immediately followed by a 0.5 mcg/kg/hour maintenance infusion. Dose Level 2 consisted of a 1.0 mcg/kg loading dose immediately followed by a 0.75 mcg/kg/hour maintenance infusion. The dosing scheme is demonstrated in Figure 1 below. The loading dose was administered over 10 minutes and the maintenance infusion commenced immediately following completion of the loading dose.

**Figure 1 DEX-11-01 Study Schematic**




Rescue Medications:
Rescue medications were administered during DEX administration to treat inadequate sedation (midazolam) and pain (fentanyl). Subjects could also receive midazolam (MDZ) or fentanyl when severe anxiety, agitation, or pain was anticipated. At any time based on clinical need or investigator's discretion, DEX could be discontinued and the

subject converted to an alternative therapy. In the event of premature discontinuation, post-infusion PK samples would be obtained and 24-hour follow-up procedures initiated.

Sedation level was assessed using the UMSS; pain was assessed using the Faces, Legs, Activity, Cry & Consolability (FLACC) scale.

*Midazolam*
If, in the opinion of the Investigator or designee, the subject was not adequately sedated, as defined by a UMSS score of 2 to 4, rescue midazolam (MDZ) could be bolused at dose of 0.05 – 0.1 mg/kg. While the package insert recommends 2 to 3 minutes between doses, dosing intervals were left to the discretion of the investigator. A UMSS would be obtained within 5 minutes prior to and 5 minutes after administration of MDZ, and subjects requiring more than four doses of MDZ per hour were considered treatment failures and discontinued from the study.

*Fentanyl*
If the subject had a FLACC score > 4 or if the opinion of the Investigator or designee was that the subject was in pain and rescue analgesia was required, the subject could receive fentanyl by intermittent bolus or continuous intravenous infusion. If given as a bolus, a FLACC score was recorded within 5 minutes prior to and within 5 minutes following the fentanyl bolus, and the fentanyl dose was recorded as well. If given as an infusion, a FLACC score was obtained with the scheduled vital signs every four hours, and pain assessments were collected within 5 minutes prior to and within 5 minutes following each titration. The recommended dose of fentanyl was 1-4 mcg/kg bolus every 2-4 hours or 1-3 mcg/kg/hour infusion.

Concomitant Medications:
Use of the following medications was prohibited during the DEX infusion period:

- Sedatives and analgesics other than DEX, MDZ, and fentanyl.
- Acetaminophen/ibuprofen except administered as antipyretics in the presence of fever.
- NSAIDs except for the management of patent ductus arteriosus.
- Neuromuscular blocking agents, except when bolused periodically to facilitate painful interventions. If neuromuscular blocking agents were administered prior to the start of the study, the subject must be clinically clear of paralytic effects, as gauged by spontaneous movement, pharmacologic reversal, or passage of a six hour wash-out period.
- Any drugs contraindicated with the use of DEX, MDZ, or fentanyl.
- $\alpha_2$- agonists/antagonists other than DEX (listed in Appendix B of 16.1.1 Protocol and Protocol Amendments, within Module 5.3.4.2.4).
- Anesthetic or analgesic agents administered spinally or epidurally.

<u>Populations</u>

Sample Size:
The planned sample size was six subjects, or three per dose level, all at one study site. Five subjects were randomized and all five completed treatment. The protocol specified that the Sponsor could elect to discontinue enrollment after successful completion of the study by five subjects.

Inclusion Criteria:

(1) Subject is 12 months to < 24 months of age at screening.
(2) Subject is intubated and mechanically ventilated in an intensive care setting and is anticipated to require a minimum of 6 hours of continuous IV sedation.
(3) Subject has adequate renal function, defined as: Serum creatinine ≤ 1.0 mg/dL.
(4) The subject's parent(s) or legal guardian(s) must voluntarily sign and date the informed consent document approved by the Institutional Review Board.

Exclusion Criteria:

(1) Pediatric subjects with neurological conditions that prohibit an evaluation of sedation such as:
    a. Diminished consciousness from increased intracranial pressure
    b. Extensive brain surgery (surgery requiring intracranial pressure monitor)
    c. Diminished cognitive function per Principal Investigator (PI) discretion
    d. Subjects with immobility from neuromuscular disease or continuous infusion of neuromuscular blocking agents.
(2) Subjects with second degree or third degree heart block unless subject has a permanent pacemaker or pacing wires are in situ.
(3) Subjects who have hepatic impairment as defined by a SGPT/ALT >90 U/L at the time of Screening.
(4) Subjects who have hypotension, based on repeat assessments within 15 minutes preceding the start of study drug, defined as: SBP < 70 mmHg.
(5) Pre-existing bradycardia based on repeated assessments within 15 minutes preceding the start of study drug, defined as: HR < 70 bpm.
(6) Subject who have acute thermal burns involving more than 15 percent total body surface area.
(7) Subjects who have a known allergy to dexmedetomidine, MDZ or fentanyl.
(8) Subject who has received dexmedetomidine within 15 hours prior to the start of study drug.
(9) Subjects with a life expectancy that is < 72 hours.
(10) Subjects that are expected to have hemodialysis (continuous hemofiltration), peritoneal dialysis or extracorporeal membrane oxygenation (ECMO) treatments within 48 hours prior to the start of study drug or during the duration of the study.
(11) Subjects who have been treated with α-2 agonists/antagonists within two weeks.
(12) Subjects with a spinal cord injury above T5.

(13) Subjects who have received another investigational drug as part of an investigational drug study within the past 30 days.
(14) Subjects who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of this clinical study.

Endpoints and Analyses

Endpoints:
Primary and secondary endpoints were not defined in the protocol. However, given the primary objective of defining DEX pharmacokinetics and pharmacodynamics, endpoints can be abstracted from the PK and PD variables identified in parts 4.4 and 4.5 of the statistical analysis plan.

The pharmacokinetic profile of DEX was assessed through the following parameters:

- AUC (area under the plasma concentration-time curve)
- Cmax (observed peak plasma concentration)
- Css (steady state concentration)
- CL (plasma clearance)
- λz (Terminal-phase elimination rate constant)
- Tmax (observed time reach maximum plasma concentration, expressed in hours)
- t1/2 (terminal half-life)
- Vd (volume of distribution)
- Vss (volume of steady state distribution)

The pharmacodynamic profile of DEX was assessed through the following parameters:

- Sedation score (UMSS)
- Time to first use rescue MDZ for sedation
- Pain score (FLACC)
- Total amount of rescue fentanyl
- SBP
- MAP
- HR
- RR
- $SpO_2$

Changes in Protocol or Planned Analyses

Protocol Amendments:
Changes to the protocol were made once during the study. The final amended clinical protocol was compiled on 5 July 2011.

*Amendment 1 (5 Jul 2011)*
The 5 July 2011 amendment incorporated the changes listed below, adapted from Appendix G (Protocol Amendment: List of Changes).

1. Exclusion Criteria was amended to exclude subjects who had received subjects within 15 rather than 24 hours prior to study drug initiation.

Changes outlined in Administrative Letter #1, dated 3 June 2011, and Administrative Letter #2, dated 23 June 2011, were also incorporated into the 5 July 2011 amendment, as follows:

1. For internal protocol consistency, the timing of ECG and labs was changed in 6.13 (Post-Study Drug Administration) from 24 hours to 10 hours after DEX discontinuation.
2. The required documentation of protocol deviations was clarified, such that not all protocol deviations need be recorded on CRFs. Investigators were to contact the Applicant in the event of protocol deviations, and the types of deviations not requiring CRF documentation were not defined. However, example deviations that the Applicant stated "should be noted in the subject's source documentation and may not be required to be captured on the deviation CRF/eCRF page include:
    - Early/late pharmacokinetic blood draw collections
    - Early/late completion of study procedures
3. Data collection means was changed from paper to electronic CRFs.
4. The Applicant changed the study design to obtain assessment scores for UMSS rather than FLACC within 5 minutes of obtaining each PK sample.

Statistical Analysis Plan Amendments:
The final SAP, dated 29 July 2011 and amended 8 Aug 2011, is provided in Appendix 16.1.9. The SAP changes follow:

1. Dose timing periods were clarified, e.g. 0 – 6 hours was changed 0 - <6 hours.
2. The applicant reportedly omitted the analysis description from the original SAP text but had included, in the SAP Table of Contents table, the following:
    - Descriptive statistics for FLACC scores while on study drug will be summarized using all FLACC scores for a subject.
    - The time to first dose of rescue medication for sedation and analgesia will be summarized with Kaplan Meier estimates.
3. Removed were plots of mean plasma concentrations vs. time curve (1) during study drug infusion period by dose level and (2) post-study drug infusion by dose level. The Applicant stated that the graphs would not be useful because the sample collection times and infusion duration varied between subjects.
4. Added to the Table of Contents for tables were the following:

- 14.2.7.1 Individual and Summary of Pharmacokinetic Parameters Full Evaluable Population.
- 14.2.7.1 Individual and Summary of Pharmacokinetic Parameters Safety Population.

5. Added to the Table of Contents for figures were the following:
    - 1.1 Pharmacokinetic Parameters Versus Age Full Evaluable Population.
    - 1.2 Pharmacokinetic Parameters Adjusted for Weight Versus Age Full Evaluable Population.

**Medical Reviewer Comments:**
This single-center study was conducted in order to meet the PWR Amendment #1 pharmacokinetic study requirement of 12 subjects in the 12 to < 24 month age range; these five subjects augmented the seven CHOP subjects.

**Study W98-266**

A Phase I, Multi-Center, Open-Label Study Evaluating the Pharmacokinetics and Pharmacodynamics of Dexmedetomidine in Pediatric Patients

Objectives

Primary Objectives:
- To evaluate the pharmacokinetics of a single intravenous dose of dexmedetomidine in pediatrics.
- To evaluate the safety of dexmedetomidine. Safety assessments will include physical examinations, routine laboratory profiles, monitoring the incidence of adverse events, and the monitoring of vital signs.

Secondary Objectives:
- To evaluate the level of sedation, using a 4-point sedation scale for pediatric patients.
- To evaluate hemodynamic and vital signs response in children, including heart rate, blood pressure, oxygen saturation, and respiratory rate.

Design

W98-266 was a Phase I, multi-center, open label study in pediatric patients between two and twelve years of age, evaluating the safety, pharmacokinetics, and pharmacodynamics of DEX in up to 18 pediatric patients requiring general anesthesia for surgery and an overnight hospitalization. The study consisted of three ascending

dose groups with six patients per group. Within each group, four subjects would receive DEX and two subjects would serve “no treatment” observational controls. DEX dosing would commence two hours before induction of anesthesia.

Treatments and Interventions

Test Treatments:
DEX was administered intravenously for 10 minutes at the following rates:

- 2 mcg/kg/hour for Group 1
- 4 mcg/kg/hour for Group 2
- 6 mcg/kg/hour for Group 3

Populations

Sample Size:
According to the protocol, a sample size of up to 18 subjects was originally chosen for pharmacokinetic evaluation without formal sample-size calculations. However, the protocol was amended to allow a second enrollment site and double total possible enrollment numbers. Therefore, 36 subjects were enrolled, with 18 at each of two sites.

Inclusion Criteria:

(1) Patient and/or legally acceptable representative (if acceptable by local law and acceptable to Ethics Committee) has signed and dated the Informed Consent after the study has been fully explained.
(2) Pediatric patient must be between the ages of 2 and 12 years of age.
(3) Patient is undergoing a surgical procedure requiring general or general and epidural anesthesia, and an overnight stay in the hospital in a monitored setting is required.

Exclusion Criteria:

(1) Patient has serious CNS trauma (that has a potential to affect level of consciousness).
(2) Patient has undergone or requires intracranial surgery during current hospitalization. .
(3) Patient who requires pre-medication (i.e. midazolam) except sevoflurane for insertion of intravenous catheters per the guideline specified in section 7.2.2.
(4) Patient in whom propofol is contraindicated, or has known or suspected serious allergy to any medication that might be administered during the course of the study.
(5) Patient is obese (body weight is greater than 50% above the ideal body' weight for height).
(6) Patient who is currently using any enzyme inducing drugs.

(7) Patient in whom alpha-2 agonists or alpha-2 antagonists are contraindicated.
(8) Patient is currently being treated or has been treated within the last 30 days with alpha-2 agonists or antagonists.
(9) Patient who has participated in a trial with any experimental drug within 30 days prior to the start of the study.
(10) Terminally ill patients, whose life duration expectancy is no more than or around 24 hours.
(11) Patient has previously received dexmedetomidine.
(12) Patient has unstable or uncontrolled diabetes.
(13) Patient has excessive bleeding.
(14) Patient who received anti-histamine medications or other medications for sedation (e.g. phenobarbital, midazolam, etc.) within 12 hours prior to study drug infusion, except for sevoflurane for insertion of intravenous catheters per the guidelines specified in section 7.2.2.
(15) Patient has any other condition or factor which, in the Investigator's opinion, might increase the risk to the patient or preclude obtaining satisfactory study data.

Endpoints and Analyses

Primary and secondary endpoints were not defined in the protocol. However, given the primary objectives of evaluating DEX pharmacokinetics and safety, endpoints can be abstracted from the variables defined in 9.5.5, Pharmacokinetic Variables, within the study report and in 10.6, Other Safety Variables, within the protocol.

Pharmacokinetic parameters for assessing the dexmedetomidine's pharmacokinetic profile:

- $C_{max}$ (maximum observed plasma concentration)
- Peak time, $T_{max}$ (time to the maximum observed concentration)
- β (terminal elimination rate constant)
- $AUC_t$ (area under the plasma concentration-time curve from time zero to the time of the last measurable concentration)
- $AUC_{ext}$ (area under the plasma concentration-time curve extrapolated to infinite time)
- $AUC_\infty$ (area under the plasma concentration-time curve from time zero to infinity)
- CL (plasma clearance)
- MRT (mean residence time)
- $V_{ss}$ (steady-state volume of distribution)

Safety variables:

- Vital signs
- Oxygen saturation

- Cardiac monitoring
- Concomitant medications

Changes in Protocol or Planned Analyses

The protocol was amended three times during the conduct of the study and once prior to study initiation. Changes affecting the conduct of the study follow:

*Amendment 2 (16 Jun 1999)*

- Instructions regarding other medications were changed such that benzodiazepines and other non-opioid sedatives would be avoided.
- Epidurally administered local anesthetics could include epinephrine if subjects had plastic surgery.

*Amendment 3 (18 Oct 1999)*

- The study design was changed from single-center to multi-center.
- Vecuronium was added to rocuronium as an acceptable neuromuscular blocking drug.
- Exclusion criterion was changed from subjects requiring premedication to subjects requiring premedication except sevoflurane for intravenous catheter insertion.

# 6 Review of Efficacy

## ***Efficacy Summary***

In essence, (b) (4) both failed to demonstrate their primary endpoint. DEX-08-05 was a dose-controlled, assessor-blinded trial and represented the older pediatric subjects; its failed primary endpoint was a difference in the percentage of subjects not receiving rescue midazolam. DEX 09-08 was a dose-controlled open-label trial in the youngest pediatric age group; its failed primary endpoint was a difference in the incidence of midazolam rescue.

(b) (4) confounded by frequent administration of concomitant medications that the Applicant did not account for. Using a narrow definition of "rescue" that was limited to midazolam, the Applicant greatly underestimated the amount of rescue medications administered. Moreover, the Applicant only collected detailed information regarding those medications they considered as rescue, namely midazolam administered under certain circumstances, and the absence of details about many of the other 11,000 medications in the concomitant medications dataset makes determination of the clinical effect of the study drug impossible.

Also problematic was the Applicant's analysis (b) (4) based primarily upon the (b) (4) Evaluable" population, which consisted of subjects who received DEX for a minimum of six hours. Many of the subjects who received DEX for less than six hours were prematurely discontinued because of an inadequate clinical effect. Their exclusion from the (b) (4) analysis leads to inaccurate conclusions about the adequacy of DEX for the (b) (4)

Finally, clinical trials of sedation medications are difficult to design, and the data have been difficult to interpret. Therefore, FDA is currently involved in discussions with experts in the study of sedation. For further discussion of the challenges faced with designing and interpreting sedation trials that is relevant to this supplement, the reader is referred to the FDA's Clinical Development Programs for Sedation Products Public Workshop website (http://www.fda.gov/Drugs/NewsEvents/ucm301022.htm).

## 6.1 Indication

The current labeling for DEX related to ICU sedation states the following:

*Precedex® is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting...The efficacy, safety, and pharmacokinetics of Precedex in pediatric patients less than 18 years of age have not been established. Therefore, Precedex should not be used in this population.*

With Supplements 21 and 22, (b) (4)

### 6.1.1 Methods

A total of six studies were submitted for review (b) (4). Efficacy was a primary endpoint for three of the studies, DEX-08-05, DEX-09-08, and DEX-11-06. The other three studies, CHOP, DEX-08-01, and DEX-11-01, evaluated the pharmacokinetics (PK) and pharmocodynamics (PD) of DEX, and the PD (b) (4)

### 6.1.2 Demographics

The six studies were moderately well balanced by gender, but not by race.

There was a small predominance of males, which is somewhat expected, as males in the pediatric age group are more likely to undergo surgery than females in the pediatric age group. When all the trials were pooled, the difference in enrollment between males and females was only twelve percent, but the difference in the number of randomized subjects between gender groups within a single trial was as small as eight percent and as large as 33 percent. In all but DEX-11-06 and DEX-08-01, more males than females were enrolled (Table 14).

**Table 14 Demographics by Study - Safety Population**

| Variable | Study | | | | | | All Studies Combined |
|---|---|---|---|---|---|---|---|
| | DEX-08-05 | DEX-09-08 | DEX-11-06 | CHOP | DEX-08-01 | DEX-11-01 | |
| | N = 175 | N = 36 | N = 6 | N = 38 | N = 59 | N = 5 | N = 319 |
| Gender (%) | | | | | | | |
| Male | 57.7 | 66.7 | 33.3 | 55.3 | 45.8 | 60 | 55.8 |
| Female | 42.3 | 33.3 | 66.7 | 44.7 | 54.2 | 40 | 44.2 |
| Age (years) | | | | | | | |
| Mean | 2.6 | 0.03 | 0.02 | 0.72 | 7.39 | 1.44 | 2.9 |
| Std. Deviation | ± 3.814 | ± 0.030 | ± 0.026 | ± 0.408 | ± 4.157 | ± 0.249 | ± 1.11 |
| Race (%) | | | | | | | |
| American Indian or Alaska Native | 3.4 | | | | 1.7 | | 2.2 |
| American Indian or Alaska Native/Caucasian | 0.6 | | | | | | 0.3 |
| Asian | 1.1 | | | 2.6 | | | 0.9 |
| Black or African American | 16 | 2.8 | | 26.3 | 10.2 | | 14.1 |
| Caucasian | 72 | 80.6 | 83.3 | 60.5 | 79.7 | 80 | 73.4 |
| Caucasian/Asian | | | | 2.6 | 1.7 | | 0.6 |
| Caucasian/Black | 0.6 | 2.8 | 16.7 | | 1.7 | | 1.3 |
| Caucasian/Hispanic | | | | | 1.7 | | 0.3 |
| Caucasian/Indian | | | | 2.6 | | | 0.3 |
| Caucasian/Lebanese | 0.6 | | | | | | 0.3 |
| Native Hawaiian or Other Pacific Islander | 0.6 | | | | | | 0.3 |
| Other | 5.1 | 13.9 | | 5.3 | 3.4 | 20 | 6 |
| Race (%) | | | | | | | |
| Caucasian | 73.7 | 83.3 | 100 | 65.8 | 84.7 | 80 | 76.5 |
| Non-Caucasian | 26.3 | 16.7 | | 34.2 | 15.3 | 20 | 23.5 |

Regarding racial distribution, the large majority of subjects were Caucasian (76.5%), with a range between 61.8% to 87% for the different age groups. The second largest

overall group was Black/African American, representing 14.1% of all subjects and between 2.4% and 25.5% of the different age groups. The remaining 12.5% of subjects were classified as Other, American Indian of Alaska Native, Asian, or Native Hawaiian or Other Pacific Islander.

### 6.1.3 Subject Disposition

Overall, there were not many subjects who discontinued treatment early or dropped out of the clinical trials, and the evaluation of subject disposition is reassuring. The subject dispositions for the six trials are summarized below (Table 15).

**Table 15 Subject Disposition**

| Study | DEX-08-05 | DEX-09-08 | DEX-11-06 | CHOP | DEX-08-01 | DEX-11-01 |
|---|---|---|---|---|---|---|
| Consented | 205 | | 7 | 38 | 69 | |
| Randomized/ ITT Population | 175 | 36 | 6 | 38 | | 5 |
| Safety Population | 175 | 36 | 6 | 38 | 59 | 5 |
| Completed Treatment | 164 | 36 | 6 | 36 | 56 | 5 |
| Completed Study | 150 | | | 35 | | |
| PK Evaluable Population | | 22 | | 36 | 57 | |
| Discontinued Study | 22 | 0 | | | 3 | |
| Lost to Follow-up | 13 | | | | | |
| AE | 3 | | | 1 | 2 | |
| Death | 4 | | | 1 | | |
| Physician Reason | 3 | | | | 1 | |
| Other* | 1 | | | | | |

* "Other" = data were inadvertently not collected for subject who was on DEX less than 2 hours (Subject 25325 [low dose])

Considering DEX-08-05, the largest of the trails, the only disposition-related concerns were the absence of documentation of reasons for non-randomization after consent, and the 22 subjects who didn't complete the study.

Reasons for exclusion of 30 consented DEX-08-05 subjects were not presented in the submission. Limited information indicated that two parents withdrew consent, one subject had a midazolam allergy, one had elevated LFTs, and one had hypotension. Information regarding the other excluded subjects would aid in determining the generalizability of the DEX-08-05 data.

A somewhat large number of subjects, 22 or eleven percent, did not complete the study. Fourteen of the subjects were lost to follow-up. In addition, two subjects, who had been early discontinuations, and four subjects, who had died, were not contacted at 28 days. Among the 16 subjects who were not followed-up and not known to have died,

distribution between low and high dose groups and lower and higher age groups were fairly even, as demonstrated in Table 16. The most notable inconsistency between the group studied and the group lost to follow-up is that eight of the sixteen were enrolled by a single investigator, who had been, with 30 subjects randomized, the highest enroller in the study.

**Table 16 Number of DEX-08-05 Subjects Lost to Follow-up by Subgroup**

| | Group 1 Low Dose | | | Group 2 High Dose | | |
|---|---|---|---|---|---|---|
| | s/p CPB[a] | Other Dx[b] | Total | s/p CPB[c] | Other Dx[d] | Total |
| | N = 36 | N = 53 | N = 89 | N = 37 | N = 49 | N = 86 |
| Age group I | 2 of 25 | 3 of 38 | 5 of 63 | 3 of 26 | 2 of 34 | 5 of 60 |
| Age group II | 1 of 11 | 3 of 15 | 4 of 26 | 2 of 11 | 0 of 15 | 2 of 26 |
| Total | 3 of 36 | 6 of 53 | 9 of 89 | 5 of 37 | 2 of 49 | 7 of 86 |

CPB = cardiopulmonary bypass; Dx = diagnosis.
[a] DEX dose: Loading dose (LD) = 0.2 mcg/kg; Maintenance dose (MD) = 0.025 – 0.5 mcg/kg/hour
[b] DEX dose: LD = 0.3 mcg/kg; MD = 0.05 – 0.5 mcg/kg/hour
[c] DEX dose: LD = 0.5 mcg/kg; MD = 0.1 – 0.7 mcg/kg/hour
[d] DEX dose: LD = 0.6 mcg/kg; MD = 0.2 – 1.4 mcg/kg hour

### 6.1.4 Analysis of Primary Endpoint(s)

*Primary Trials*

**Study DEX-08-05**

The primary endpoint for DEX-08-05 was the percentage of subjects that do not require rescue midazolam for sedation based on achieving and maintaining a target UMSS score of 1-3 while intubated. The endpoint was consistent with the PWR specification, "The primary efficacy analysis will be the percentage of subjects who do not require rescue midazolam for sedation based on achieving and/or maintaining the protocol-specified sedation range..." Dexmedetomidine's current labeling for ICU sedation is based on study of a related primary endpoint, namely the amount of rescue medication required to achieve a specified level of sedation using a sedation scale, and, in one of the studies, a secondary endpoint equivalent to the DEX-08-05 primary endpoint. Therefore, the primary endpoint is consistent with DEX's previous approval and appropriate from a regulatory perspective.

The table below demonstrates the low number and percent of subjects not requiring rescue midazolam, as defined by the Applicant, and a small difference between groups. Considering the total number of subjects by dose group and across age groups, the percentage of subjects not requiring midazolam rescue ranged between 12.5 to 58% when incorporating ASA class into one's analysis group and between 27 and 57% when pooling ASA classes. The Applicant claims that overall, the high dose groups were better sedated, with percentages not requiring rescue of 54 in the high dose group

versus 45 in the low dose group. However, this difference is not statistically significant or clinically significant.

**Table 17 Number and Percent of Subjects Not Requiring Rescue MDZ for Sedation during the Treatment Period While Intubated - (b) (4) Evaluable**

Age Group
Age Group
Total
[a] Number
and main
[b] Age grou
[c] Age grou
Source: To

Group 1 Low Dex dose is LD = 0.2/ MD = 0.025 – 0.5 mcg/kg/hour
Group 1 High Dex dose is LD = 0.3/MD = 0.05 – 0.5 mcg/kg/hour
Group 2 Low Dex dose is LD = 0.5/MD = 0.1 – 0.7 mcg/kg/hour
Group 2 High Dex dose is LD = 0.6/MD = 0.2 – 1.4 mcg/kg/hour
Age group I = ≥1 month to <24 months;
Age group II = ≥24 months to <17 years old
Source: Study 08-05 CSR, Table 10 p. 71

**Study DEX-09-08**

The percentages of subjects requiring rescue in the DEX-09-08 subjects, who were ≥ 28 to ≤ 44 weeks of age, did not decrease with increasing DEX, and therefore, study failed to demonstrate its primary endpoint, although only a small percentage of subjects in this very young population received rescue MDZ (Table 18).

**Table 18 Percentages of Subjects in DEX-09-08 who Received Rescue MDZ for Sedation - (b) (4) Evaluable Population[4]**

| Number and Percent of Subjects[a] | Dose Level 1 DEX 0.05[c] N = 14 | Dose Level 2 DEX 0.1[c] N = 14 | Dose Level 3 DEX 0.2[c] N = 8 | Total (N = 36) |
|---|---|---|---|---|
| Age Group I[b] | 0/6 (0.0%) | 0/6 (0.0%) | – | 0/12 (0.0%) |
| 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%) | 1/14 (7.1%) | 2/8 (25.0%) | 4/36 (11.1%) |

Source: Table 14.2.1.1
[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).
DEX=Dexmedetomidine; kg=kilogram; mcg=microgram; MDZ=midazolam

Source: Study DEX-09-08 CSR, Table 10, p.63

The Applicant's determination of percentage of subjects requiring rescue medication did not account for subjects receiving fentanyl, and including fentanyl in the analysis greatly increases the incidence of rescue above that claimed by the Applicant. Moreover, fentanyl was sometimes administered for an indication of sedation. Regardless of its dose justification, fentanyl administration decreased the likelihood that a subject would need midazolam for rescue. Table 19 demonstrates fentanyl administration during DEX, and at least a few of these should probably be considered sedation rescue.

**Table 19 DEX-09-08 Subjects Receiving Fentanyl Infusion or Fentanyl for Sedation but Not Counted as Needing Rescue**

| Subject | Age Group[a] | DEX Dose[b] | Fentanyl Indication | Dose | Dose Interval |
|---|---|---|---|---|---|
| 119111002 | I | 0.05 | Sedation | 1 mcg/kg/hr | Continuous |
| 102213001 | II | 0.1 | Discomfort associated with ventilator | 4 mcg | Continuous |
| 100223008 | II | 0.1 | Pain/agitation | 3.5 mcg prn | PRN q1 hr |
| 100122013 | I | 0.1 | Pain | 2 mcg/kg/hr | Continuous |
| 102223003 | II | 0.1 | Postoperative pain management | 9.18 mcg/hr | Continuous |
| 100213004 | II | 0.05 | Pain | 1 mcg/kg/hr | Continuous |
| 100223007 | II | 0.1 | Pain | 1 mcg/kg/hr | Continuous |

Derived from DEX-09-08: CM.xpt and ADSL.xpt
[a] Age group I = ≥ 28 to < 36 weeks gestational age; Age group II = ≥ 36 to ≤ 44 weeks.
[b] DEX dose in mcg/kg for loading dose and mcg/kg/hr for maintenance dose
DEX=Dexmedetomidine; kg=kilogram; mcg=microgram; hr=hour

[4] The Sponsor had declared the (b) (4) Evaluable population as the population for the primary analysis

**Study DEX-11-06**

The primary efficacy endpoint for DEX-11-06 was the frequency of subjects requiring any use of rescue MDZ for sedation during DEX infusion, which was claimed to be zero despite several rescue fentanyl administrations. According to the Applicant, no subject received rescue MDZ for sedation during Study Drug Infusion[5]. However, analysis of the concomitant medications datasets revealed one subject with an order for MDZ for "agitation" during DEX, and one subject with a fentanyl infusion for "pain and agitation" during DEX. A third subject received fentanyl boluses for pain during DEX. These subjects demonstrate that, (b) (4) subjects in this study needed rescue during DEX.

[5] Study 11-06 CSR, p.42.

*Supporting PK or PD Studies*

**CHOP Study**

The CHOP study did not declare a primary efficacy variable, and it failed to demonstrate a clinical response to increasing DEX, although the high rate of fentanyl administration makes interpretation of the sedation data difficult. All subjects in the highest dose group except one required fentanyl, and 64 percent received midazolam whereas 25 percent of subjects in the low dose group and 58 percent in the middle dose group received midazolam in the post-operative period, which was defined by the Applicant as the 48 hour period after surgery. However, subjects' DEX infusions may have been discontinued at any time during the 48 hour period, and therefore the data represents administration of additional sedatives and analgesics regardless of persistent DEX infusion. Nonetheless, the increasing need for MDZ with increasing DEX dose does not favor increased effect with increased DEX.

**Table 20 CHOP Summary of Post-Operative Additional Sedation and Analgesia - Safety Population – (b) (4) Evaluable Population**

| | Low Dose[a] N=12 | Moderate Dose[b] N=12 | High Dose[c] N=14 | P-Value[d] |
|---|---|---|---|---|
| Patients with analgesia medication, n (%) | 12 (100.0) | 12 (100.0) | 13 (92.9) | 1.0000 |
| Fentanyl (mcg) | | | | |
| n | 6 | 5 | 2 | |
| Mean (SD) | 12.25 (12.962) | 113.45 (221.674) | 10.60 (6.987) | |
| Median (Min, Max) | 6.00 (5.0, 50.0) | 15.00 (5.0, 643.0) | 8.50 (5.0, 30.0) | |
| Morphine sulfate (mcg) | | | | |
| n | 11 | 12 | 13 | |
| Mean (SD) | 423.65 (190.630) | 515.10 (176.312) | 493.33 (173.215) | |
| Median (Min, Max) | 400.00 (250.0, 1000.0) | 500.00 (200.0, 1000.0) | 520.00 (200.0, 800.0) | |
| Patients with sedation medication, n (%) | 3 ( 25.0) | 7 ( 58.3) | 9 ( 64.3) | 0.1467 |
| Midazolam (mcg) | | | | |
| n | 3 | 7 | 9 | |
| Mean (SD) | 456.00 (307.620) | 353.39 (228.616) | 446.15 (90.050) | |
| Median (Min, Max) | 300.00 (290.0, 1000.0) | 400.00 (0.1, 800.0) | 400.00 (300.0, 600.0) | |

Source: Table 14.3.6.3.2

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-value from Fisher's Exact Test.

Max=maximum, min=minimum, N, n=number of patients, SD=standard deviation

Source: CHOP Study Table 22, p. 79

**Study DEX-08-01**

DEX-08-01 was a PK study without a primary efficacy endpoint for analysis, and the incidence of rescue midazolam did not consistently decrease with increasing DEX administration. However, the incidence of rescue midazolam administration does not does not fully represent concomitant sedating medication administration; also administered were doses of chloral hydrate for sedation and agitation, lorazepam for agitation, methadone for sedation, and propofol for sedation. Classifying these medications as rescue greatly increases the rate of rescue administration, and leads to greater question regarding the reliability of DEX as a sedative in this population.

**Table 21 DEX-08-01 Percentage of Subjects Who Received Rescue MDZ for Sedation During Treatment Period While Intubated by Dose Level and Age Group – (b) (4) Evaluable Population**

| Parameter/ Statistics | Dose Level 1 DEX N=16 | Dose Level 2 DEX N=13 | Dose Level 3 DEX N=14 | Dose Level 4 DEX N=14 | P-value |
|---|---|---|---|---|---|
| Group I (n[%]) | 4 (50.0) | 4 (66.7) | 3 (50.0) | 1 (16.7) | 0.2446[b] |
| Group II (n[%]) | 3 (37.5) | 3 (42.9) | 2 (25.0) | 2 (25.0) | 0.5110[b] |
| Total Age Group (n[%]) | 7 (43.8) | 7 (53.8) | 5 (35.7) | 3 (21.4) | |
| P-values for Differences[a] | 1.0000 | 0.5921 | 0.5804 | 1.0000 | |
| Overall (CMH Test) Value[c] | | | | | 0.9997 |
| Raw Mean Scores Differ DF | | | | | 1 |
| Prob | | | | | 0.3174 |

Source: Table 14.2.2.3
Abbreviations: CD=continuous dose; CMH=Cochran-Mantel-Haenszel; DEX=dexmedetomidine; LD=loading dose; MDZ=midazolam
Note: Group I: Ages ≥2 through 6 years old; Group II: Ages ≥ 6 through 17 years old.
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] Differences between age Groups I and II within each dose level using Fisher's exact test.
[b] P-value of Cochran-Armitage trend test within age group.
[c] CMH test with a strata age group.
Source Study DEX-08-01 CSR Table 11, p. 57.

**Study DEX-11-01**

As with the other pharmacokinetic studies described above, DEX-11-01 did not have a primary endpoint, (b) (4)
Pharmacodynamic assessments included use of rescue midazolam and fentanyl, and the sponsor reported in the CSR an overall 40 percent rate of midazolam use and a 60 percent rate of fentanyl use (Table 22). Only two of the five subjects did not receive midazolam or fentanyl, and both were tracheostomy and ventilator dependent and scored as deeply sedated by UMSS prior to DEX infusion initiation. While the sample size was very small, these data suggest that a subject may need to be deeply sedated prior to DEX initiation and that DEX may be an ineffective sedative agent in subjects with intact airway reflexes.

**Table 22 DEX-11-01 Percentage of Subjects who Received Rescue Midazolam or Fentanyl during DEX infusion – Safety Population**

| | DEX Dose Level 1 N =2 | DEX Dose Level 2 N = 3 | Total N = 5 |
|---|---|---|---|
| Midazolam | 1 (50%) | 1 (33.3%) | 2 (40%) |
| Fentanyl | 1 (50%) | 2 (66.7%) | 3 (60%) |

Abbreviations: CD=continuous dose; DEX=dexmedetomidine; LD=loading dose;
Note: Dose Level 1 – DEX LD=0.7mcg/kg; CD=0.5mcg/kg/hour
Dose Level 2 – DEX LD=1 mcg/kg; CD=0.75 mcg/kg/hour

**Study W98-266**

W98-266 was a pharmacokinetic study of a bolus infusion of DEX. There was no rescue medication given and no pharmacodynamic assessments comparable to those described above were obtained.

### 6.1.5 Analysis of Secondary Endpoints(s)

***Primary Supporting Trials***

**Study DEX-08-05**

Multiple secondary endpoints existed for DEX-08-05, and DEX-08-05 failed at those endpoints in addition to failing its primary endpoint. The secondary endpoints included the absolute time and percentage of time on study drug that the subjects 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.

While the reported time in UMSS range was relatively high, the analysis was biased because it only included those subjects who received DEX for at least six hours. Therefore, the analysis didn't include subjects in whom the drug was discontinued during the first six hours of treatment due to inadequate sedative effect, and inclusion of those subjects in the analysis would have decreased the apparent effectiveness of the drug.

Per the Applicant, percentage of time within the UMSS range was determined by a linear interpolation between consecutive measurements to estimate the time within the UMSS range 1 to 3 and time above or below that range. In every group presented, the percentage of time spent in the target range was >85%, with the lowest percentage among subjects s/p cardiopulmonary bypass in the low dose group. However, there was no statistically significant difference between groups for either time or percentage of time spent in the target sedation range, and no dose-response correlation.

**Table 23 DEX-08-05 Median Absolute Time and Percentage of Time in UMSS Range 1-3 During the Treatment Period While Intubated - Efficacy Evaluable Population**

Age Gr
…Age Gr

Other Dia
Age Gr
…Age Gr

[a] Median
[b] Age gr
[c] Age gr

Source: Table 14.2.2.3, dex-08-05-study-report-body

**Study DEX-09-08**

Like DEX-08-05, DEX-09-08 failed to demonstrate its primary endpoint, and the value in analyzing the secondary endpoints is questionable. Secondary efficacy endpoints were incidence of rescue medication (fentanyl or morphine) for analgesia, amount of rescue midazolam for sedation, amount of rescue medication for analgesia, changes from baseline in vital signs, time with N-PASS score >3, and time from study drug administration to extubation. The data suggest a lack of dose-response, as the percentage of subjects requiring rescue increases with increasing dose (Table 24).

**Table 24 DEX-09-08 Subjects Receiving Rescue Fentanyl of Morphine for Analgesia - Safety Evaluable Population**

| Subjects | Dose Level 1 DEX 0.05 N = 14 | Dose Level 2 DEX 0.1 N = 14 | Dose Level 3 DEX 0.2 N = 8 | Total N = 36 |
|---|---|---|---|---|
| Number | 5/14 | 5/14 | 6/8 | 16/36 |
| Percentage | 35.7 | 35.7 | 75 | 44.4 |

Note: Units for loading dose are mcg/kg and units for infusion are mcg/kg/hour for each Dose Level.
Adapted from CSR Table 14.2.2.1.3; source data in CSR Listing 16.2.9.1.5

However, in addressing their secondary endpoint, the Applicant presented percentages of subjects receiving rescue fentanyl or morphine that do not reflect the actual number of subjects who received fentanyl of morphine. The Applicant included, as subjects receiving rescue fentanyl or morphine, only those who had an indication of pain or pain management. Five subjects with fentanyl orders during DEX for an indication of pain/agitation, discomfort associated with ventilator, postoperative pain management, or sedation were not considered as receiving rescue analgesia nor rescue sedation. These subjects should probably be included as receiving sedation rescue, analgesia rescue, or both, but the Applicant has counted them as neither.

**Study DEX-11-06**

Secondary efficacy endpoints for DEX-11-06 were identical to those of its complementary study DEX-09-08. Regarding the endpoint of incidence of rescue medication use for analgesia, the Applicant reported that one of the six subjects received fentanyl, or 16.7 percent of subjects. However, a second subject received fentanyl during DEX, and perhaps a more accurate percentage of subjects requiring rescue analgesia is 33.3.

As with DEX-09-08, the Applicant has under-represented fentanyl administration, as two of six DEX-09-08 subjects required fentanyl for analgesia. Analysis of the concomitant medication dataset revealed a subject who received a fentanyl infusion throughout study drug administration for an indication of “pain and agitation.” The summary of the

data presented by the sponsor, taken on face, would lead to the conclusion of a greater clinical effect of DEX and a lower need for rescue analgesia than actually occurred.

*Supporting PK or PD Studies*

**CHOP Study**

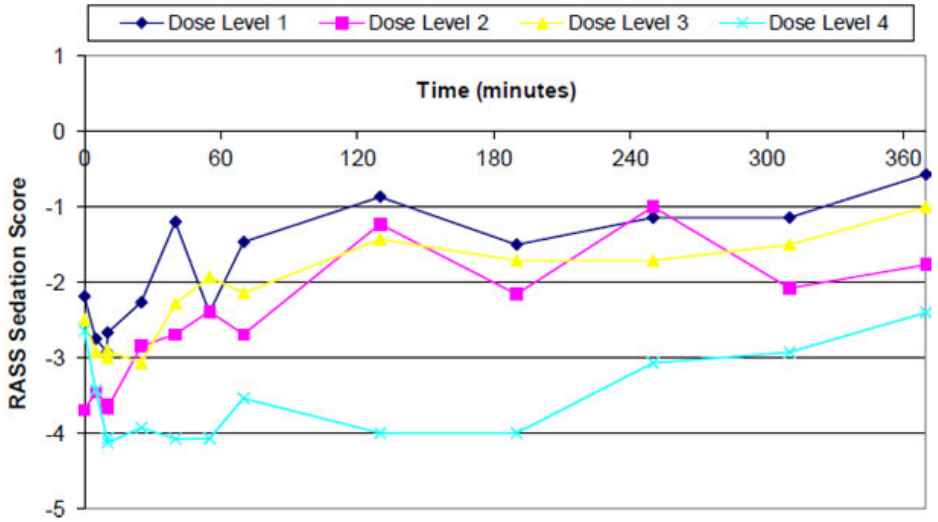
The CHOP study was a pharmacokinetic study and therefore had no pre-specified primary or secondary endpoints. However, a variety of pharmacodynamic data were collected and analyzed by the Applicant. After exploratory assessment for a potential PK/PD relationship, the Applicant concluded no correlation between serum plasma concentration of DEX and the level of sedation or plasma clearance of DEX. The Applicant also concluded that an analysis of the correlation between the UMSS scores and DEX plasma $AUC_{0-t}$ was not clinically meaningful. Statistically significant relationships were identified for a few parameters at a few time points, but possible relationships at a few select time points are not clinically meaningful.

**Study DEX-08-01**

Endpoints were not specified in the DEX-08-01 study protocol, although, as with CHOP, pharmacodynamic parameters were analyzed by the Applicant and a dose-response correlation not identified. The Applicant concluded that there was no statistically significant difference between dose groups for any parameter; these parameters were total midazolam or fentanyl dose administered per subject, weight adjusted midazolam or fentanyl dose administered per subject, and time to first rescue midazolam.

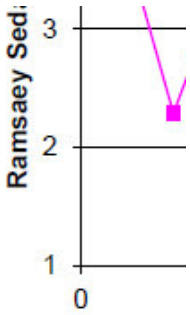
DEX-08-01 evaluated four dose groups, including one group with a uniquely high maintenance infusion rate of 0.2 mcg/kg/hour, with a notable difference in depth of sedation. However, median time to first rescue medication and the mean sedation scores over the first six hours of administration were similar between Dose Levels 2 and 3, while the loading dose was doubled and the infusion rate nearly doubled between the two groups. Graphs of sedation scores, provided by the Applicant, follow, and reveal little consistent difference between Dose Levels 1, 2, and 3, whereas Dose Level 4, a much higher dose, appears to be more effective. However, DEX-08-01 was the only study to evaluate such a high infusion rate, (b) (4)

**Figure 2 DEX-08-01 RASS Sedation Scale over 10-Minute Loading Dose and First Six Hours of Maintenance**




Dose Level 1: loading infusion 0.25 mcg/kg and maintenance infusion 0.5 mcg/kg/hour
Dose Level 2: loading infusion 0.5 mcg/kg and maintenance infusion 0.4 mcg/kg/hour
Dose Level 3: loading infusion 1 mcg/kg and maintenance infusion 0.7 mcg/kg/hour
Dose Level 4: loading infusion 1 mcg/kg and maintenance infusion 2 mcg/kg/hour

**Figure 3 DEX-08-01 Ramsay Sedation Scale over 10-Minute Loading Dose and First Six Hours of Maintenance Dose**



**Study DEX-11-01**

As with the other pharmacokinetic studies, endpoints were not defined in the DEX-11-01 protocol. However, pharmacodynamic data were collected on the five subjects, and percentage of subjects requiring fentanyl or midazolam above in 6.1.4 Analysis of Primary Endpoint(s).

Also analyzed by the Applicant and overall, (b) (4) were total and weight-adjusted amounts of rescue midazolam and fentanyl. The subject numbers were very small, but according to the CSR, subjects randomized to the lower dose of DEX required less total midazolam and more midazolam per kilogram than subjects in the higher dose group. However, subjects receiving the lower dose of DEX required slightly more fentanyl than subjects in the higher DEX dose group.

**Table 25 DEX-11-01 Mean Midazolam and Fentanyl Doses Administered Per Subject - (b) (4) Evaluable Population**

| | DEX Dose Level 1 N = 2 | DEX Dose Level 2 N = 3 |
|---|---|---|
| Midazolam (mg) | 0.5 | 3.7 |
| Midazolam (mg/kg) | 0.06 | 0.42 |
| Fentanyl (mcg) | 60 | 49.56 |
| Fentanyl (mcg/kg) | 6.62 | 5.5 |

Abbreviations: CD=continuous dose; DEX=dexmedetomidine; LD=loading dose;
Note: Dose Level 1 – DEX LD=0.7mcg/kg; CD=0.5mcg/kg/hour
Dose Level 2 – DEX LD=1 mcg/kg; CD=0.75 mcg/kg/hour

## 6.1.6 Other Endpoints

Experimental and exploratory endpoints for further study were not proposed by the Applicant. This reviewer feels the primary endpoint was reasonable and that useful information about the efficacy DEX in pediatric patients would most likely be obtained through study design modification to lessen the administration of concomitant medications, which confound interpretation of the data, and decrease the heterogeneity of doses between subjects, so that dose groups can more readily be compared.

## 6.1.7 Subpopulations

Analysis of race and gender did not reveal any clinically meaningful differences between subgroups. Some small differences between demographic groups were identified, although they were not consistent across dose groups. Their significance is also questionable given the submission's overarching problems, i.e., frequent administration of unaccounted-for sedatives and analysis based upon the (b) (4) evaluable subjects

rather than the DEX-exposed population. Nonetheless, analysis of subpopulations, as presented by the Applicant, is included in this section.

By gender, the Applicant reports no difference overall between the number of subjects requiring rescue midazolam, and higher total doses of rescue midazolam in males than females. However, the pattern of increased dose requirements among males is not consistent across age groups. The most striking value, which also has the largest standard deviations, is the relatively large midazolam dose received by non-neonatal males in the low dose group (PDL-2). The data, ultimately demonstrating no difference between genders, are presented below ().

**Table 26 Subjects Requiring Rescue Midazolam and Mean Midazolam Doses Among Subjects Receiving Midazolam by Gender - (b) (4) Evaluable Population**

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | PDL-1 N=26 | PDL-2 N=68 | PDL-3 N=73 | Total N=167 | PDL-1 N=16 | PDL-2 N=51 | PDL-3 N=61 | Total N=128 |
| Number of Subjects | 3 | 29 | 33 | 65 | 1 | 29 | 19 | 49 |
| Percent of Subjects | 11.5 | 42.6 | 45.2 | 38.9 | 6.3 | 56.9 | 31.1 | 38.3 |
| Midazolam (mg) | 0.87 | 5.83 | 3.01 | 4.17 | 0.5 | 1.71 | 2.81 | 2.11 |
| Midazolam (mg/kg) | 0.25 | 0.48 | 0.25 | 0.35 | 0.15 | 0.2 | 0.23 | 0.21 |

PDL-1: Neonatal subjects (28 wks gestational age to <1 mo); loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr
PDL-2: Subjects ≥1 month to 16 years of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr
PDL-3: Subjects ≥1 month to 16 years of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr

The Applicant divided subjects into Caucasian and Non-Caucasian groups, and while rescue midazolam administration differed between groups, a difference in requirement by race cannot be determined. Non-Caucasians were probably combined into a single group for comparison because of the small numbers of non-Caucasian subjects. Caucasians trended toward a higher incidence of midazolam rescue, but that when required by Non-Caucasians, the midazolam doses were higher, both in mg and in mg/kg. The data, as reported by the Applicant, are presented below (Table 27).

**Table 27 Subjects Requiring Rescue Midazolam and Mean Midazolam Doses Among Subjects Receiving Midazolam by Race - (b) (4) Evaluable Population**

| | Caucasian | | | | Non-Caucasian | | | |
|---|---|---|---|---|---|---|---|---|
| | PDL-1 N=36 | PDL-2 N=90 | PDL-3 N=99 | Total N=225 | PDL-1 N=6 | PDL-2 N=29 | PDL-3 N=35 | Total N=70 |
| Number of Subjects | 4 | 49 | 41 | 94 | 0 | 9 | 11 | 20 |
| Percent of Subjects | 11.1 | 54.4 | 41.4 | 41.8 | 0 | 31 | 31.4 | 28.6 |
| Midazolam (mg) | 0.78 | 3.69 | 2.43 | 3.02 | n/a | 4.18 | 4.84 | 4.54 |
| Midazolam (mg/kg) | 0.22 | 0.34 | 0.22 | 0.28 | n/a | 0.37 | 0.33 | 0.35 |

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

**Dosing Recommendations: ≥ 28 to ≤ 44 weeks**

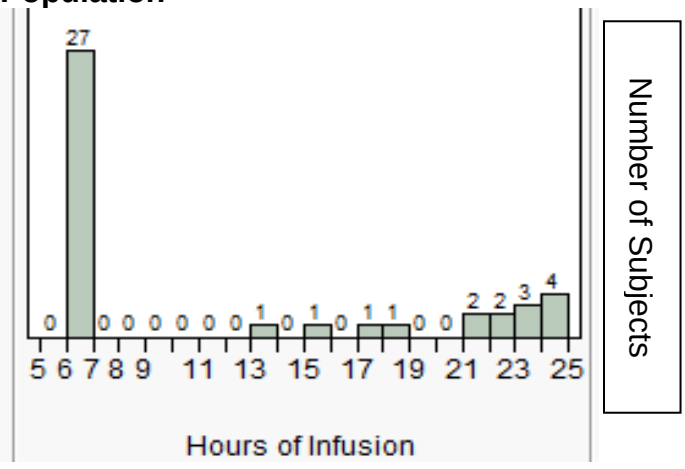
The Applicant [redacted] (b) (4) [redacted]. The two studies, considered together, had 72 power detect a 45 percent difference between low and high dose groups in the number of subjects requiring rescue midazolam.

[redacted] (b) (4) in this population are the absence of any early discontinuations and a low rate of rescue midazolam administration.

However, there was no apparent dose-response. Very little difference between the percentage of subjects requiring rescue midazolam in the high vs. low dose groups (85.7 percent in the high-dose group vs. 92.9 percent in the low and intermediate dose groups), was demonstrated, despite four times as much DEX administered in high dose group compared to the low dose group.

Not only did these two clinical trials not demonstrate a clinical effect, [redacted] (b) (4) [redacted] The [redacted] (b) (4) [redacted] However, the infusion was stopped at six hours in 27 of 42 subjects (64 percent), leaving only fifteen subjects with infusions of greater than six hours (Figure 4). In addition, of the four subjects reported by the Applicant to have received rescue midazolam, two were in the cluster of subjects with the longest infusions (>20 hours), giving an incidence of rescue midazolam of 50 percent among subjects whose infusion duration approached 24 hours. That is, per the Applicant's reported midazolam use data, the percentage of all subjects aged 28 to 44 weeks that received rescue midazolam was ten percent, whereas eighteen percent of subjects who received an infusion over 20 hours required rescue midazolam.

**Figure 4 Duration of Infusion by Subject Aged 28 to 44 Weeks - [redacted] (b) (4) Evaluable Population**



(b) (4)

The Applicant (b) (4) However, as the neonates, the Applicant failed at their primary endpoint and failed to demonstrate a dose-response, even when analyzing the (b) (4) Evaluable population with a limited definition for rescue. The Applicant provided the following table (b) (4) (Table 28).

**Table 28** (b) (4)

(b) (4)

Also considered key by the Applicant (b) (4) is the reported median percent of time in target sedation range, which is of arguable utility. This measure (b) (4) is based upon, per the Statistical Methods Analysis Plan, "a linear interpolation...to estimate the time within the UMSS range 1-3 and above or below this range. If there are several UMSS scores at one time, then the average of these scores will be used."

The derived percentage of time within the UMSS range is of arguable value for three primary reasons. First, it is a subjective measure, with large inter-observer variability. Second, it is performed at defined points in time surrounding rescue administration of fentanyl and morphine, but during DEX-08-05, there were over several hundred instances where a sedating medication was administered and the UMSS not recorded, because the protocol required UMSS documentation only around the time of DEX initiation or rescue administration, using the Applicant's narrow definition of rescue. Therefore, subjects may have been undersedated (or oversedated), and had either a

DEX dose adjustment or another sedative administered, while not having a UMSS score documented; scores taken every four hours, per the protocol, might reflect adequate sedation 100 percent of the time despite intervening periods of agitation. Third, the concept of averaging UMSS scores if several existed at once is concerning. Does the Applicant mean that scores obtained immediately before and after rescue, and therefore no more than ten minutes apart, should be averaged? If this is the case, a score of 4 immediately prior to rescue midazolam and 2 immediately after would average to a 3, and one would conclude that a subject with these scores had been in the target sedation range 100 percent of the time. Therefore, the averaging of scores taken "at one time" may be a means of increasing the apparent percentage of time in target sedation range. These three problems discount the Applicant's contention that subjects were adequately sedated approximately 95% of the time during DEX infusion.

Regarding dose selection, (b) (4) (b) (4). The (b) (4) was not covered in DEX-08-05, the only assessor-blinded clinical trial, despite being evaluated in preceding pharmacokinetic studies. Some DEX-08-05 subjects received a DEX loading dose ranging from 0.2 to 0.6 mcg/kg, but no DEX-08-05 subject received a loading dose between 0.6 and 1 mcg/kg, for (b) (4)

(b) (4) Despite not having presented methods of dose calculation in their analysis, the following table demonstrates the Applicant's mean and median maintenance DEX dose from Study DEX-08-05, which reveals a wide range of doses studied, but perhaps a reasonable representation of the (b) (4)

**Table 29 DEX-08-05 DEX Maintenance Doses per 2.7.3.4.1.2** (b) (4)

| | Mean Maintenance Dose (mcg/kg/hour) | Maintenance Dose Range (mcg/kg/hour) | Median Dose (mcg/kg/hour) |
|---|---|---|---|
| Dose Level 1 | 0.35 | 0.17-0.51 | Not given |
| Dose Level 2 | 0.64 | 0.08-1.44 | 0.62 |

All doses in mcg/kg/hour
Dose Level 1: 0.025-0.5 mcg/kg/hour maintenance dose after optional load of 0.2-0.3 mcg/kg
Dose Level 2: 0.1-1.4 mcg/kg/hour maintenance dose after optional load of 0.5-0.6 mcg/kg

Finally (b) (4) pharmacodynamic data (b) (4) at the highest infusion rate, 2 mcg/kg/hour. However, 2 mcg/kg/hour is almost three times the upper limit of the infusion rate (b) (4) The (b) (4) data, taken directly from the submission, are in Table 30 below. Note the difference in midazolam and fentanyl requirements in Dose Level 4, compared with the doses (b) (4)

(b) (4) (b) (4)

**Table 30 Key Pharmacodynamic Measures in DEX-08-01**

| Subjects | Dose Level 1 (N = 16) | Dose Level 2 (N = 13) | Dose Level 3 (N = 14) | Dose Level 4 (N = 14) |
|---|---|---|---|---|
| **Midazolam** | | | | |
| **n (%)** | 7 (43.8%) | 7 (53.8%) | 5 (35.7%) | 3 (21.4%) |
| **mg** | 2.0 (1-6) | 1.5 (1-8.8) | 6.0 (1-12.7) | 4.0 (0.8-6) |
| **Fentanyl** | | | | |
| **n (%)** | 12 (75.0%) | 10 (76.9%) | 13 (92.9%) | 8 (57.1%) |
| **mcg** | 45.2 (10-300) | 63.8 (10-45199) | 30.0 (15.5-270) | 50.7 (30-120) |
| **Median time to first rescue medication (hr) (95% CI)** | 1.0 (0.417, 3.500) | 2.2 (0.600, 3.333) | 2.5 (1.367, 3.867) | 7.8 (1.250, NE) |

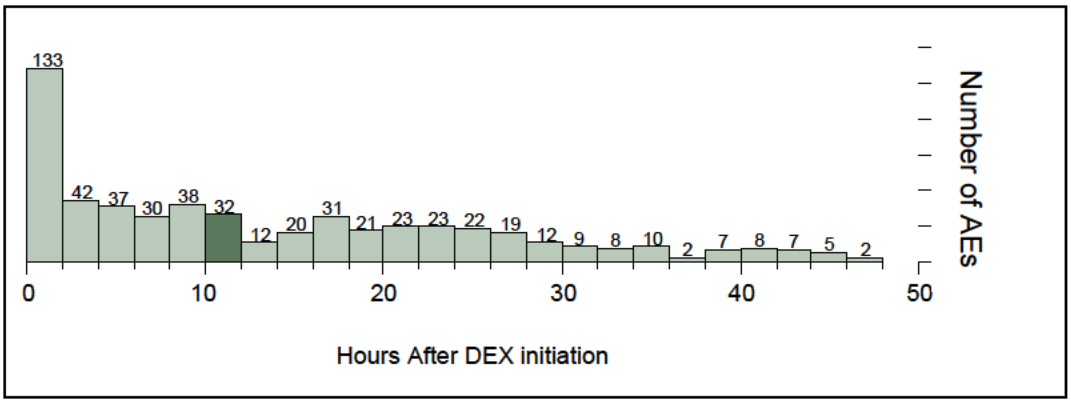
N = number of Full Evaluable subjects at given Dose Level.
n (%) = number (percent) of Full Evaluable subjects at given Dose Level who received midazolam or fentanyl.
Data presented as median (range) for midazolam and fentanyl use.
Data presented as median time (95% CI) to first dose of rescue medication.
Dose Level 1: loading dose 0.25 mcg/kg; maintenance dose 0.2 mcg/kg/hr.
Dose Level 2: loading dose 0.50 mcg/kg; maintenance dose 0.4 mcg/kg/hr.
Dose Level 3: loading dose 1.00 mcg/kg; maintenance dose 0.7 mcg/kg/hr.
Dose Level 4: loading dose 1.00 mcg/kg; maintenance dose 2.0 mcg/kg/hr.
Abbreviations: CI = confidence interval; CSR = clinical study report; hr = hour; mcg = microgram; mg = milligram; NE = non-estimatable.
Source: DEX-08-01 CSR, Table 14.2.3.1.1.1, Table 14.2.6.1.

### 6.1.9 Discussion of (b) (4) Tolerance Effects

Current DEX labeling is for use in adults for up to 24 hours, and indicates that use beyond 24 hours is associated with tachyphylaxis and a dose-related increase in adverse reactions. Therefore, the infusion durations studied for this submission were limited to 24 hours.

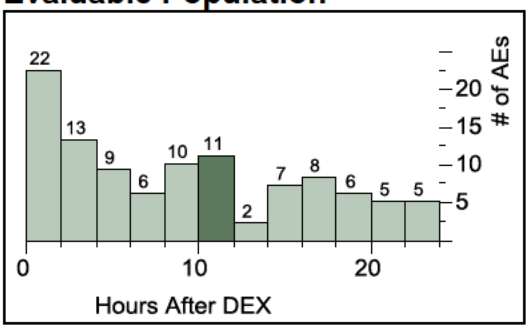
Given the understanding of DEX tachyphylaxis and increased adverse events with longer DEX infusions, the incidence of adverse events occurring after study drug initiation through 24 hours post-study drug discontinuation was evaluated. However, evidence for increased adverse event incidence with increased infusion was not identified. Instead, by far the greatest number of adverse events occurred during DEX initiation.

**Figure 5 Timing of Adverse Events - Safety Evaluable Population**




However, tachyphylaxis is most likely to reflected by an increase in adverse events when drugs are titrated to effect, and only DEX-08-05 allowed dose titration. Therefore, the following histogram reflects adverse event incidence in only DEX-08-05 subjects, who were eligible for dose titration and, on average, had upwards titration of DEX during the study period. The data do not reveal an increase in adverse events over time during DEX infusion, and therefore, do not suggest tachyphylaxis. Instead, the data are most striking for the lesser incidence of adverse events during DEX initiation compared with Figure 5. The decreased incidence of adverse events in the first two hours of DEX in DEX-08-05 compared with the all studies is likely due to DEX-08-05's optional loading dose, whereas all other studies in the safety evaluable population required the loading dose.

**Figure 6 DEX-08-05 Timing of Adverse Events during DEX Infusion - Safety Evaluable Population**



### 6.1.10 Additional (b) (4) Issues/Analyses

There were numerous issues (b) (4) in this submission. In summary, the studies were conducted in order to inform pediatric DEX dosing after issuance of a Pediatric Written Request. Limitations of the studies are described under the individual study, but the submission included data from only one blinded study, which had two dose groups, with dose titration available and a large degree of overlap between the ranges of doses administered, regardless of a subject's randomization to the high or low dose group. The Applicant failed to achieve the primary endpoint in that study and ultimately failed to demonstrate a dose-response (b) (4) Other confounding issues were the widespread administration of medications that were for rescue of sedation or that increased sedation, as a side effect, and therefore the determined primary endpoint, percent of subjects requiring rescue, was not truly reflected in the statistics reported by the Applicant (b) (4).

# 7 Review of Safety

## ***Safety Summary***

This supplement failed to demonstrate the safety of DEX for (b) (4) Two fundamental problems are inadequate documentation of vital signs and insufficient information about concomitant medication administration. Without additional information, safety of DEX for this population cannot be concluded.

**Vital Signs**

Most concerning is the absence of vital sign documentation. DEX causes hypotension in approximately 25% of adults in the intensive care unit, and hypotension was considered an adverse event of special interest in this submission. However, vital signs were not documented during adverse events, and alarmingly, vital signs during some adverse events of hypotension are unknown. For example, one of the six subjects that died had an adverse event of hypotension during DEX, and no documented blood pressure during the 100 minute hypotensive episode. The Applicant concluded that the subject's multisystem-organ failure and sepsis were unrelated to DEX; however, this reviewer contends that the in absence of important details regarding the subject's DEX-related adverse event of hypotension, it is unreasonable to conclude that DEX and did not contribute to the subject's decline and ultimate death.

In this submission, inadequate vital sign documentation leads not only to unreliable characterization of adverse events as described above, but also to an inability to describe incidence and severity of hypotension caused by the DEX. The Applicant's vital signs dataset is missing nearly ten percent of the data points that were required per

the protocol, and many subjects receiving DEX missed three consecutive scheduled vital signs measurements, thereby going without vital sign documentation for up to twelve hour during the DEX infusion.

Exploration of the available vital signs data reveals missing pieces of information in subjects with extremely low blood pressures. For example, the subject with the single lowest recorded systolic blood pressure in DEX-08-05 had no adverse events and incomplete vital sign documentation. Five minutes after DEX was discontinued, the 1.6 year-old subject with baseline blood pressure of 114/55 had a blood pressure of 52/40. The subject had missed the previous scheduled blood pressure, and therefore a six hour period without vital sign documentation preceded this episode of extreme hypotension that was not considered an adverse event.

**Concomitant Medications**

Extensively discussed in Section 6 Review of Efficacy is the absence of detailed information about concomitant medications in the setting of widespread use, which is important for both determining the contributions of other agents to sedation and for understanding severity and treatment of adverse events. One cannot reliably conclude adverse event frequencies associated with DEX use, as the adverse events the adverse events in this submission may reflect DEX little more than they reflect adverse events occurring in ICU subjects sedated with midazolam and an opioid.

The safety data in this submission may be much more a reflection of the milieu of sedatives administered in the trials than the safety profile of the study drug. Without knowing how much of these rescue medications were administered and when, one must question whether any safety conclusions can reasonably be drawn.

An important aspect of understanding adverse events' severity is understanding their management. Without information about timing and dosing of vasopressors that were administered during hypotension, the severity of these hypotensive events cannot be characterized. Unfortunately, details about medications were not collected by the Applicant, and therefore, the safety of DEX cannot be determined.

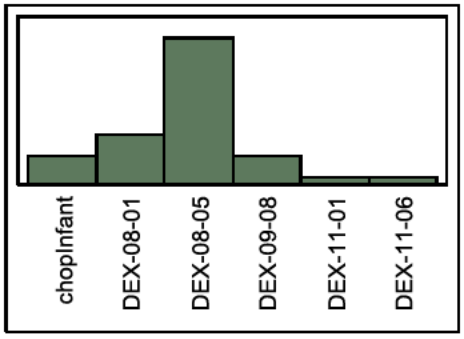
## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review of safety is primarily based upon the six studies that were also submitted (b) (4) . The distribution of consented subjects by study, is presented below (Figure 7). The key features of the studies are displayed in **Error! Reference source not found.** (Section 5.1) and described in detail in Section **Error! Reference source not found.**. There were an additional 24 subjects enrolled in W98-266, but they were

not included in the integrated safety analysis because those subjects received only a ten-minute loading dose of DEX and no subsequent infusion.

**Figure 7 Subject Distribution by Study - Consented Population**




**Frequencies**

| Level | Count |
|---|---|
| chopInfant | 38 |
| DEX-08-01 | 69 |
| DEX-08-05 | 205 |
| DEX-09-08 | 39 |
| DEX-11-01 | 7 |
| DEX-11-06 | 7 |
| Total | 365 |

### 7.1.2 Categorization of Adverse Events

Investigator adverse event terms in the Integrated Summary of Safety were coded using Medical Dictionary for Regulatory Activities (MedDRA) version14.1.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant presented the Integrated Summary of Safety (ISS) based upon the pooled safety data from six clinical trials that evaluated DEX infusions for intensive care unit (ICU) sedation. A seventh study, W98-266, evaluated DEX over a ten minute loading period; the dosing and patient populations were sufficiently different from the other six studies that the Applicant presented the W98-266 safety data separately.

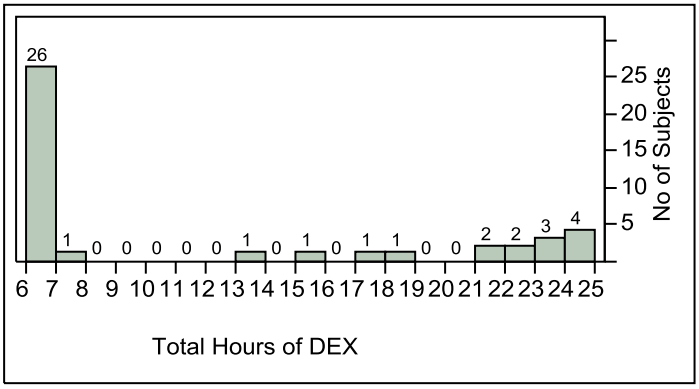
## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

(b) (4)

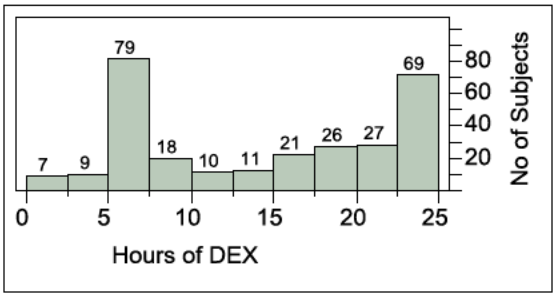
For subjects 28 to 44 weeks, the doses studied may have been adequate, but the durations were not. These subjects received fixed loading doses that were delivered over a period of 10 to 20 minutes followed by infusions of six to 24 hours duration. The histogram below (Figure 8) demonstrates that 26 of 42 subjects, or 59 percent, had DEX discontinued after six hours of administration. (b) (4) Moreover, only 11 of 42 subjects, or 26 percent, had at least 20 hours of exposure.

**Figure 8 Hours of DEX Exposure in 28 to 44 Week Gestational Age Subjects**



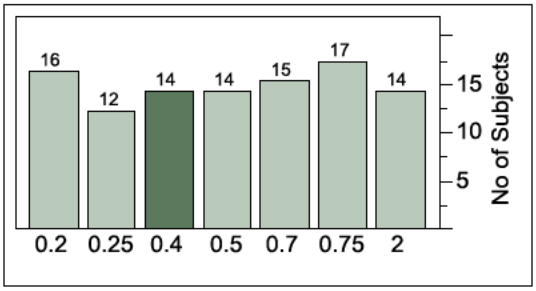

(b) (4) Specifically, only 69 of 177 subjects received DEX for at least 20 hours, (b) (4)

**Figure 9 Hours of DEX Exposure in Subjects One Month of Age and Older - Safety Evaluable Population**




The maintenance doses evaluated in subjects over one month of age seem to reflect a reasonable distribution within the range of maintenance doses [redacted] DEX-08-05 allowed for dose titration, but 84 percent of subjects received maintenance doses within the [redacted] and mean infusion rates were 0.35 and 0.64 in the two groups (Table 29). The maintenance doses for the other five trials are presented below; 71 of 102 subjects were [redacted]

**Figure 10 Number of Subjects per Fixed Infusion Rate in Subjects One Month of Age and Older - Safety Population**

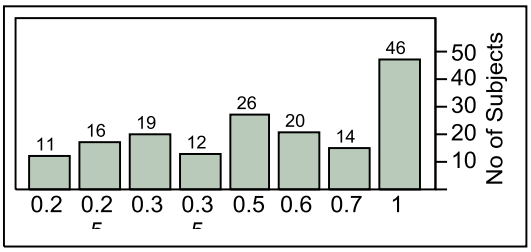



**Frequencies**

| Level | Count | Prob |
|---|---|---|
| 0.2 | 16 | 0.15686 |
| 0.25 | 12 | 0.11765 |
| 0.4 | 14 | 0.13725 |
| 0.5 | 14 | 0.13725 |
| 0.7 | 15 | 0.14706 |
| 0.75 | 17 | 0.16667 |
| 2 | 14 | 0.13725 |
| Total | 102 | 1.00000 |

For subjects greater than [redacted] and the adequacy of the loading doses to which subjects in the safety population were exposed is arguable. Two thirds of the studied loading doses [redacted] (**Error! Reference source not found.**). However, only 164, or 59 percent, of subjects received a loading dose. Moreover, only 28 percent of subjects that received a loading dose [redacted] and no subjects received a higher loading dose. Conversely, 51 percent of subjects received a loading infusion [redacted]. The remaining 21 percent of subjects received DEX loads [redacted] although in all cases on the low end of the range.

**Figure 11 DEX Loading Doses Administered in Subjects One Month of Age and Older – Safety Population**




## 7.2.2 Explorations for Dose Response

The following table provides a count, by clinical trial type, of subjects exposed to DEX by age. It demonstrates that the majority of subjects were enrolled in an assessor-blinded, dose-titration study. It also reveals that the youngest of subjects were only enrolled in open-label studies. Finally, the table includes subjects in W98-266, the single-dose study that was conducted only in older subjects.

**Table 31 Enumeration of Subjects**

| Clinical Trial Groups | 28wks to 44wks | 1mo to 16 yrs |
|---|---|---|
| **PK/PD Studies** | | |
| Single Dose | | 24 |
| Infusion | 36 | 102 |
| Subtotal | 36 | 126 |
| | | |
| **Efficacy Studies** | | |
| Active Control (Dose-Controlled) | | |
| Open-Label, Fixed Dose | 36 | |
| Assessor-Blinded, Flexible Dose | | 175 |
| Uncontrolled | 6 | |
| Subtotal | 42 | 175 |
| | | |
| Single Dose Subtotal | | 24 |
| Multiple Dose Subtotal | 42 | 278 |
| Grand Total | 42 | 302 |

## 7.3 Major Safety Results

### 7.3.1 Deaths

Six subjects died, and although all deaths occurred at least 24 hours after DEX administration, several cases may have been associated with DEX, but the information for determining causality is insufficient. The Applicant, however, denies that deaths were related to DEX administration. A table of SAEs in subjects who died, modified from Applicant's ISS Table 92, is depicted below, and a discussion of the death cases that that may have been related to DEX, in order from most to least concerning, follows ().

**Table 32 Subjects with a Serious Adverse Event with an Outcome of Death - Safety Population**

| Subject | PDL Group | Sex | Race | Day of Death* | Serious Adverse Event with Outcome of Death |
|---|---|---|---|---|---|
| CHOP-005 | 2 | M | CA | (b) (6) | Death |
| DEX-08-0-103117 | 2 | F | CA | | Renal Failure |
| | | | | | Cardiac Failure |
| DEX-08-05-14302 | 2 | M | CA | | Sepsis |
| | | | | | Multi-organ Failure |
| DEX-08-05-25315 | 2 | M | CA | | Respiratory Failure |
| DEX-08-05-25316 | 3 | F | BL | | Hypoxic Ischemic Encephalopathy |
| DEX-09-08-105121001 | 1 | M | BL | | Neonatal Respiratory Failure |

*Day of death refers to Study Day
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with loading dose 0.05 – 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.25 – 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.5 – 1 mcg/kg and maintenance dose 0.5 – 2 mcg/kg/hr.
Abbreviations: BL = Black; CA = Caucasian; F = Female; M = Male; PDL = Pediatric Dose Level.
Source: 5.3.5.3 ISS Table 92, p. 154

DEX-08-05 Subject 14302

Subject 14302 had an episode of hypotension during DEX that may have contributed to the subject's death, and during which no vital signs were recorded. Subject 14302 was a six-month male who underwent surgery for hypoplastic left heart syndrome, received DEX during a 24 hour period on post-operative days (POD) (b) (6) and died of multisystem organ failure and sepsis on (b) (6). The period of DEX administration was complicated by an adverse event of hypotension. The hypotension was classified as moderate by the investigator and warranted halting of the DEX infusion. However, no blood pressures no recorded, and no details regarding treatment interventions provided.

Seventy-two hours after the DEX-attributed hypotensive episode, an AE of increased BUN was recorded, and the subject never recovered. He had been in the low-dose group, had not received a loading dose, and was not classified as s/p cardiopulmonary bypass.

The blood pressures observed during the hypotensive episode while on DEX, and the period of DEX interruption cannot be deduced by this reviewer from the CRF or the datasets. However, it is plausible that the DEX-caused hypotension led to renal injury, manifest as uremia two days later, progressed to multisystem organ failure and death, whereas the Applicant denies relationship between the DEX administration and DEX.

DEX-08-05 Subject 103117

Subject 103117 had no vital sign documentation during twelve hours of DEX treatment, and died (b) (6) days later of cardiac and renal failure. The subject should have had blood pressure recorded every four hours during DEX and with each of a number midazolam administrations. However, no blood pressure was recorded between DEX hour 12, when the blood pressure was 104/59, and DEX discontinuation at hour 24, when blood pressure was 81/58. This reviewer is very concerned about the hemodynamic events of the 12 hour period during DEX infusion and their possible contribution to the subject's death, but the data to understand what occurred during that time was not provided. It also seems unlikely that a subject would die suddenly of cardiac and renal failure, with no preceding or precipitating adverse event, yet according to the Applicant, Subject 103117 had no adverse events until the day of her death

DEX-08-05 Subject 25315

Subject 25315 had incomplete vital sign documentation and died of respiratory failure three days after DEX discontinuation. He was a 6-month old male with a medical history of "spinal muscular atrophy," admitted for RSV pneumonia. Like Subject 103117, Subject 25315 had DEX administered for 24 hours, but for twelve of those hours, no vital signs were recorded, despite protocol-required vital signs every four hours during DEX. It seems unlikely that DEX administration would have been related to later development of respiratory failure, but in the absence of the required vital signs data and more detail about the subject's course, the absence of a relationship between DEX and the subject's death should not be assumed.

CHOP Subject 005

Subject 005 had an episode of hypertension during DEX that may have contributed to his death. Subject 005 was a 20-month male who received DEX 0.35 mcg/kg followed by 0.25 mcg/kg/hour for approximately six hours, and died after withdrawal of care on Study Day (b) (6) However, the events leading to withdrawal of care occurred within 24 hours of DEX initiation. On Study Day 1, the subject had DEX infused for 6 hours. During and in the first few hours after DEX, the subject experienced AEs of hypertension and tachycardia, graded as mild by the investigator. On Study Day 2,

subject hemorrhaged and was coded, with events were attributed to pacing wire removal. The subject was placed on ECMO and had CT and EEG scans on Study Day 2, revealing hypoxic ischemic encephalopathy. While the death occurred (b) (6) later, it is plausible that hypertension may have been related to the hemorrhage that lead to cardiac arrest, hypoxic ischemic encephalopathy, and ultimate withdrawal of care.

Death Demographics

In terms of demographics, it is notable that all subjects that died were < 2 years of age, whereas 41% of the safety population was ≥ 2 years of age. There were no other commonalities among subjects; subjects were of a mixture of races, genders, and dose groups. Only one subject was classified as s/p cardiopulmonary bypass. None of the deaths occurred during DEX, and the interval between cessation of DEX and death varied widely.

### 7.3.2 Nonfatal Serious Adverse Events

The only clear trends in serious adverse events (SAEs) are a predominance of cardiac and vascular disorders and an increased incidence among subjects one month to two years of age. However, the Applicant's incidence and classification of adverse events cannot be verified in the absence of vital sign documentation and the in absence of details about concomitant medication administration.

Twenty-nine subjects had nonfatal SAEs, including the six subjects who ultimately died during the studies. They are listed in the following table, and include a wide variety of events. However, a large number of the SAEs were cardiovascular disorders, which is not surprising given the large number of subjects s/p cardiac surgery, and the potential seriousness of cardiac events in general.

**Table 33 Non-Fatal Serious Adverse Events - Safety Population**

| Subject Number | Timing of Onset | System Organ Class | Preferred Term |
|---|---|---|---|
| CHOP 002 | MD | Vascular DO | Hypotension |
| CHOP 005 | Post-SD | Vascular DO | Haemorrhage |
| | Post-SD | General DO | Death |
| CHOP 006 | Post-SD | Cardiac DO | Coronary Artery Stenosis |
| | Post-SD | Cardiac DO | Ventricular Fibrillation |
| | Post-SD | Vascular DO | Thrombosis |
| | Post-SD | Cardiac DO | Complete Atrioventricular Block |
| CHOP 014 | MD | Vascular DO | Haemorrhage |
| CHOP 033 | Post-SD | Procedural Complication | Endotracheal Intubation Complication |

| | | | |
|---|---|---|---|
| CHOP 034 | LD | Vascular DO | Hypotension |
| CHOP 036 | LD | Nervous System DO | Sedation |
| DEX-08-01 521002 | MD | Nervous System DO | Convulsion |
| DEX-08-05 01904 | Post-SD | Cardiac DO | Bradycardia |
| DEX-08-05 02213 | Post-SD | Infectious & Infestations | Rhinovirus Infection |
| DEX-08-05 033059 | Post-SD | Surgical Procedures | Catheter Removal |
| DEX-08-05 099035 | Post-SD | Respiratory, Thoracic DO | Pulmonary Embolism |
| DEX-08-05 103117 | Post-SD | Renal & Urinary DO | Renal Failure |
| | Post-SD | Cardiac DO | Cardiac Failure |
| DEX-08-05 11203 | Post-SD | Infectious | Incision Site Infection |
| DEX-08-05 13902 | Post-SD | Immune System DO | Kidney Transplant Rejection |
| DEX-08-05 14302 | Post-SD | Infectious & Infestations | Sepsis |
| | Post-SD | General DO | Multi-organ Failure |
| DEX-08-05 15304 | MD | Cardiac DO | Myocarditis |
| DEX-08-05 16301 | Post-SD | Cardiac DO | Bradycardia |
| | Post-SD | Vascular DO | Hypotension |
| DEX-08-05 20201 | Post-SD | Investigations | Blood Culture Positive |
| DEX-08-05 21202 | Post-SD | Infectious & Infestations | Abscess Limb |
| DEX-08-05 21205 | Post-SD | Vascular DO | Arterial Limb Thrombosis |
| DEX-08-05 21206 | MD | Respiratory, Thoracic DO | Apnoea |
| DEX-08-05 25315 | Post-SD | Respiratory, Thoracic DO | Respiratory Failure |
| DEX-08-05 25316 | Post-SD | Nervous System DO | Hypoxic-Ischaemic Encephalopathy |
| DEX-08-05 26244 | Post-SD | Metabolism, Nutrition DO | Failure to Thrive |
| DEX-08-05 27309 | Post-SD | Infectious & Infestations | Meningitis |
| DEX-08-05 27804 | Post-SD | Respiratory, Thoracic DO | Pleural Effusion |
| DEX-09-08 100223007 | Post-SD | Cardiac DO | Cardiac Arrest |
| DEX-09-08 105121001 | Post-SD | Cardiac DO | Bradycardia |
| | Post-SD | Cardiac DO | Cardio-respiratory Arrest |
| | Post-SD | Investigations | Oxygen Saturation Decreased |
| | Post-SD | Respiratory, Thoracic DO | Neonatal Respiratory Failure |

DO = disorder; LD = during loading dose, MD = during maintenance dose, Pre-SD = pre-study drug administration, Post-SD = post-study drug administration

Serious adverse events seemed to be most common in the one month to two year age group. Only two subjects in the neonatal group of 42 had SAEs, and both were in the intermediate dose group. Twenty-seven subjects over the age of one month had SAEs, with not much difference in incidence according to dose group, but a difference existed according to age; 13 percent of subjects less than two years of age had an SAE, whereas 4.5 percent of subjects two years and older had an SAE. Nine of the subjects had SAEs during DEX administration, and three of these had a severe SAE during DEX. Seven of the nine subjects with treatment-emergent SAEs were aged one month to two

years. Four subjects had SAEs leading to study drug discontinuation, and three of them were aged one month to two years. SAEs by Pediatric Dose Level are summarized in Table 34 below.

**Table 34 Overview of Serious Adverse Events by Pediatric Dose Level - Safety Population**

| Subjects with Type of Serious Adverse Event | PDL-1 Neonatal (N = 42) n (%) | PDL-2 (N = 131) n (%) | PDL-3 (N = 146) n (%) | DEX Total (N = 319) n (%) |
|---|---|---|---|---|
| Subjects with one or more SAEs | 2 (4.8%) | 14 (10.7%) | 13 (8.9%) | 29 (9.1%) |
| Subjects with one or more treatment-emergent SAEs | 1 (2.4%) | 4 (3.1%) | 4 (2.7%) | 9 (2.8%) |
| Subjects with one or more severe treatment-emergent SAEs | 1 (2.4%) | 2 (1.5%) | 0 (0.0%) | 3 (0.9%) |
| Subjects with one or more drug-related SAEs[1] | 0 (0.0%) | 1 (0.8%) | 3 (2.1%) | 4 (1.3%) |
| Subjects with one or more drug-related treatment-emergent SAEs[1] | 0 (0.0%) | 1 (0.8%) | 3 (2.1%) | 4 (1.3%) |
| Subjects with SAE with outcome of death | 1 (2.4%) | 4 (3.1%) | 1 (0.7%) | 6 (1.9%) |
| Subjects with treatment-emergent SAE with outcome of death | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Subjects who discontinued study drug for one or more treatment-emergent SAEs | 0 (0.0%) | 1 (0.8%) | 3 (2.1%) | 4 (1.3%) |
| Subjects with one or more treatment-emergent SAEs of special Interest[2] | 1 (2.4%) | 1 (0.8%) | 1 (0.7%) | 3 (0.9%) |
| Subjects with one or more treatment-emergent SAEs of special Interest requiring intervention[3] | 1 (2.4%) | 0 (0.0%) | 1 (0.7%) | 2 (0.6%) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with the particular event.
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr.
(1) Drug related includes certain, definitely related, possible, possibly and probably related to study drug.
(2) Includes bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, hypotension, diastolic hypotension, hypertension, diastolic hypertension, and systolic hypertension.
(3) Includes bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, hypotension, diastolic hypotension, hypertension, diastolic hypertension, and systolic hypertension of sufficient severity to require medical intervention.
Abbreviations: hr = hour; kg = kilogram; mcg = microgram; PDL = pediatric dose level; SAE = serious adverse event.
Source: End-of-Text Table 5.1.1.

The Applicant has separately calculated incidence of treatment-emergent SAEs, which are those SAEs that occurred during DEX or within 24 hours of DEX discontinuation. The very low incidence is apparent in the Table 35, but the reliability of the Applicant's count of eleven treatment-emergent SAEs is questionable. Two examples of subjects with treatment-emergent adverse events that could have been considered serious but lacked sufficient detail are discussed below.

**Table 35 Incidence of Treatment-Emergent SAEs by Pediatric Dose Level - Safety Population**

| Treatment-Emergent SAE SOC Preferred Term | PDL-1 Neonatal (N = 42) n (%) | PDL-2 (N = 131) n (%) | PDL-3 (N = 146) n (%) | DEX Total (N = 319) n (%) |
|---|---|---|---|---|
| Number of Events | 3 | 4 | 4 | 11 |
| Number of Subjects with Any Event | 1 (2.4%) | 4 (3.1%) | 4 (2.7%) | 9 (2.8%) |
| Cardiac Disorders | | | | |
| Bradycardia | 1 (2.4%) | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Cardio-Respiratory Arrest | 1 (2.4%) | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Myocarditis | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 1 (0.3%) |
| Investigations | | | | |
| Oxygen Saturation Decreased | 1 (2.4%) | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Nervous System Disorders | | | | |
| Convulsion | 0 (0.0%) | 1 (0.8%) | 0 (0.0%) | 1 (0.3%) |
| Sedation | 0 (0.0%) | 0 (0.0%) | 1 (0.7%) | 1 (0.3%) |
| Respiratory, Thoracic, and Mediastinal Disorders | | | | |
| Apnea | 0 (0.0%) | 0 (0.0%) | 1 (0.7%) | 1 (0.3%) |
| Vascular Disorders | | | | |
| Hemorrhage | 0 (0.0%) | 1 (0.8%) | 1 (0.7%) | 2 (0.6%) |
| Hypotension | 0 (0.0%) | 1 (0.8%) | 1 (0.7%) | 2 (0.6%) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with the particular event.
Each subject is counted only once per SOC when multiple preferred terms are reported for the SOC.
A subject reporting same event multiple times is counted only once for the event.
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr.
Abbreviations: hr = hour; kg = kilogram; mcg = microgram; PDL = pediatric dose level; SOC = System Organ Class; SAE = serious adverse event.
Source: End-of-Text Table 5.3.1.

DEX-08-05 Subject 14302

Subject 14302, who was also discussed in Section 7.3.1 Deaths, did not have a treatment-emergent SAE according to the Applicant. His “moderate hypotension” was deemed “probably related” to DEX and, according to the AE dataset, led to interruption of DEX. However, no data was recorded in the vital signs data set nor on the CRF from this period of moderate hypotension, and the patient subsequently developed uremia and ultimately multisystem organ failure and death. While it cannot be definitively concluded that DEX initiated the subject’s cascade of events by causing hypotension that led to renal injury, the lack of detailed, accurate information surrounding this hypotensive event leads one to conclude that it probably constitutes a treatment-emergent SAE. This example calls to question the data presented by the Applicant and their low reported incidence of treatment-emergent SAEs.

DEX-08-05 11203

According to the narrative summary provided by the Applicant, Subject 11203 had an uneventful hospitalization and a later SAE of sternal wound infection that was unrelated to DEX, and but the information is insufficient to rule out a relationship. Review of the AE dataset reveals that during the DEX infusion, subject had "low CVP reading" requiring treatment; the concomitant medication dataset indicates plasmanate was administered for treatment of this AE. However, the subject also had epinephrine and milrinone infusions that were started at unknown times on the day of DEX initiation. In addition, thirty-five minutes before the AE onset, the DEX dose was halved, which seems not in keeping with the protocol but also was not considered a protocol violation. And no vital signs were recorded until two hours after the decrease in DEX dose. The narrative summary does not acknowledge any issue with the hospitalization, but something significant obviously took place during DEX, causing a halving of the subject's infusion. The details around the event, which could have contributed to the subject's later sternal wound infection, are absent from the submission.

### 7.3.3 Dropouts and/or Discontinuations

The number of dropouts and discontinuations in the study was not large, although the common themes are inadequate sedation and hypotension. However, review of the dropouts and discontinued subjects raises concerns about the quality and reliability of the data reported. Nonetheless, all dropouts and discontinuations were at least one month of age, and therefore, discussion of disposition is therefore limited to subjects at least one month of age. Subject disposition is reported by the Applicant in the table below (Table 36). It should be noted that although the Applicant indicated that16 subjects prematurely discontinued treatment, 24 subjects were identified in the ADSL dataset as early discontinuations.

**Table 36 Subject Disposition by Pediatric Dose Level - Safety Population**

| Subject Disposition | PDL-1 Neonatal (N = 42) n (%) | PDL-2 (N = 131) n (%) | PDL-3 (N = 146) n (%) | DEX Total (N = 319) n (%) |
|---|---|---|---|---|
| Subjects who completed study | 42 (100%) | 116 (88.5%) | 133 (91.1%) | 291 (91.2%) |
| Subjects who discontinued study | 0 (0%) | 15 (11.5%) | 13 (8.9%) | 28 (8.8%) |
| Reason for study discontinuation | | | | |
| Adverse event | 0 (0%) | 4 (3.1%) | 2 (1.4%) | 6 (1.9%) |
| Does not meet/No longer meets entry criterion | 0 (0%) | 1 (0.8%) | 0 (0%) | 1 (0.3%) |
| Physician reason | 0 (0%) | 2 (1.5%) | 1 (0.7%) | 3 (0.9%) |
| Investigator's discretion | 0 (0%) | 0 (0%) | 1 (0.7%) | 1 (0.3%) |
| Investigator reason: Leaking PIV | 0 (0%) | 0 (0%) | 1 (0.7%) | 1 (0.3%) |
| Lost to follow-up | 0 (0%) | 6 (4.6%) | 7 (4.8%) | 13 (4.1%) |
| Other | 0 (0%) | 2 (1.5%) | 1 (0.7%) | 3 (0.9%) |
| | | | | |
| Subjects who completed treatment | 42 (100%) | 125 (95.4%) | 136 (93.2%) | 303 (95.0%) |
| Subjects who discontinued treatment | 0 (0%) | 6 (4.6%) | 10 (6.8%) | 16 (5.0%) |
| Reason for treatment discontinuation* | | | | |
| Adverse event | 0 (0%) | 0 (0%) | 4 (2.7%) | 4 (1.3%) |
| Lack of efficacy | 0 (0%) | 1 (0.8%) | 2 (1.4%) | 3 (0.9%) |
| Subject's medical condition changes and requires deeper level of sedation | 0 (0%) | 1 (0.8%) | 0 (0%) | 1 (0.3%) |
| Physician reason | 0 (0%) | 0 (0%) | 1 (0.7%) | 1 (0.3%) |
| Other | 0 (0%) | 2 (1.5%) | 0 (0%) | 2 (0.6%) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with the particular disposition.
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr.
*The reasons for treatment discontinuation for studies DEX-08-01 and the CHOP study were not collected.
Abbreviations: PDL = pediatric dose level; PIV = peripheral intravenous (line).
Source: End-of-Text Table 1.1.

Discontinuations Related to Hypotension

The following four discontinuations were related to hypotension, and are part of the hypotension signal that has been identified in the submission.

DEX-08-05 Subject 27303 was a 1.4 year-old randomized to high-dose DEX who did not undergo cardiopulmonary bypass and had DEX discontinued after 0.7 hours due to physician request. The subject's blood pressure had declined from a baseline of 99/48 to 76/31, after which the study drug was discontinued. The lowest systolic blood pressure provided by the Applicant was 70/39, and occurred 5 minutes after DEX discontinuation. Per the protocol, a systolic blood pressure < 70 mmHg for subjects > 6 months to < 2 years of age is a dose-limiting toxicity and an adverse event. However,

no hypotensive adverse event was reported to have taken place and the subject was lost to follow-up.

CHOP Subject 034 was a four-month-old male who received high-dose DEX had a non-fatal SAE of hypotension and hemorrhage that immediately followed the DEX loading dose, at which time the investigator discontinued the DEX. The hypotension was graded as moderate in severity, and treated with fluid, blood products, and Factor VIIa; the subject recovered without sequelae.

CHOP Subject 024 received DEX at an intermediate dose (falling into PDL-3) for 3.1 hours, and approximately two hours into the infusion, had an AE of hypotension that was graded as mild and unlikely to be related to DEX. The subject had further bouts of hypotension, all of which were graded as mild and occurred more than 72 hours after DEX was discontinued. This leads to the conclusion that the early episode of hypotension may have been related to DEX despite the investigator's judgment otherwise.

CHOP Subject 023 received DEX at an intermediate dose (falling into PDL-3) for 5.6 hours, and DEX was discontinued due to onset of complete atrioventricular block that was considered possibly related to DEX. No blood pressure or heart rate during the event was reported. The event was graded as moderate in severity and was of only one minute in duration. The subject had no similar subsequent events and no apparent sequelae related to the event and completed the study.

Discontinuations Related to Inadequate Drug Effect

Discussed below are a number of premature discontinuations related to possible or probable inadequate drug effect. Cases of hypertension are included because hypertension is frequently a manifestation of inadequate sedation, although these cases of hypertension cannot necessarily be attributed to DEX because of insufficient information.

Subject DEX-08-05-24304 was a 1.4 year-old randomized to low-dose DEX and did not undergo cardiopulmonary bypass whose DEX was discontinued after 2.1 hours due to lack of efficacy. The subject did not have any AEs.

Subject DEX-08-05-599004 was a 2.3 year-old randomized to high-dose DEX who did not undergo cardiopulmonary bypass had DEX discontinued after 4.1 hours due to lack of efficacy. The subject did not have any adverse events recorded and completed the study.

Subject DEX-08-05-20211 was randomized to the high-dose group, and did not receive a loading DEX dose, but after 3.7 hours of DEX, developed agitation, due to which DEX was discontinued. On study day 2, the subject developed moderate hypoxia, but no

other AEs were reported. As with the subjects described above, with the exception of two doses of midazolam, the timing and precise doses of concomitant medications were not provided, limiting this reviewer's ability to well-characterize the degree of rescue administered, although the Applicant reports none.

Subject DEX-08-05-25325 was a 1.8 year-old randomized to low-dose DEX who did not undergo cardiopulmonary bypass whose DEX was discontinued after 1.9 hours due to a need for deeper sedation for change in medical condition; the condition requiring deeper sedation was not identified, but the subject received three doses of midazolam during the less than two hours that she received DEX. This subject's only adverse events were hypocalcemia and hypoalbuminemia, with onset prior to DEX administration, and the subject was discontinued from the study at an unknown time. She had no documented medications administered and seemingly was not followed to any extent, to include having vital signs recorded, after the DEX discontinuation, whereas the follow-up period should have been 28 days after the informed consent was signed.

Subject DEX-08-05-31224 was a 0.4 year-old randomized to high-dose DEX who underwent cardiopulmonary bypass and had DEX discontinued after 4.8 hours due to physician reason. Lorazepam was initiated and three doses of midazolam were administered during DEX, although information about the precise timing of lorazepam administration and number of administrations was not provided in the dataset or the narrative. Subject 31224 had five adverse events: low potassium, third degree heart block, and pyrexia all occurred prior to DEX initiation, and adverse events of rhinovirus infection and tachyarrhythmia started more than four days after DEX discontinuation and are therefore; the adverse event are unlikely to be related to the study drug. This reviewer believes the most likely rationale behind the physician's decision to discontinue DEX was also the reason for the midazolam rescue, that is, agitation.

DEX-08-05 Subject 11202 was randomized to the low-dose DEX group, but DEX was discontinued after only approximately two hours of infusion because of no intravenous access. In this subject with congenital heart disease, one would expect adequate intravenous access, although line discontinuation may have been related to lack of efficacy or to the AE of pneumothorax. However, the concomitant medication datasets do not indicate that any of the subject's infusions were discontinued at the time of the AE, and actual times of medications administered to this subject relative to DEX dosing were not provided. The subject's other AEs that developed within approximately six hours of DEX discontinuation were mild pulmonary edema, moderate hyperglycemia, and moderate hypokalemia.

Subject DEX-08-05-31322 was a 1.2 year-old randomized to low-dose DEX who did not undergo cardiopulmonary bypass and had DEX discontinued after 2.75 hours due to subject extubation and, according to the narrative, no longer required sedation. However, the subject had a midazolam infusion and a prn midazolam order that were initiated during study drug administration, leading one to question the accuracy of the

statement that the subject “no longer required sedation.” The subject’s only recorded adverse events were hypo- and hyperkalemia that occurred well-before and after the DEX infusion. This subject was considered by the Applicant as not having required rescue, but leads this reviewer to conclude a high likelihood that DEX was ineffective in adequately sedating the subject. The subject did not complete the study for “physician reason”.

DEX-08-05 Subject 11201 had an moderately severe adverse event of post-operative hypertension that required treatment; the onset was just prior to low-dose DEX initiation and it persisted twelve hours beyond the DEX stop time. DEX may have been discontinued due to lack of efficacy, its inadequate sedative effect is evidenced by the apparent administration of midazolam rescue and pancuronium during the DEX infusion. However, precise information about the medications administered, to include doses and times of doses, was not provided by the Applicant and therefore a definitive conclusion about the subjects slightly early withdrawal and its implications for safety cannot be drawn.

CHOP Subject 037 was an 8 month old who received high-dose DEX for two hours before DEX was discontinued due to a leaking PIV. This DEX end time was preceded by an AE of hypertension with onset 22 minutes earlier. It is believable that DEX was discontinued due to lack of intravenous access, as there appear to have been no intravenous medications given over 90 minutes after the DEX discontinuation. However, it is very unlikely that a subject would undergo surgery requiring cardiopulmonary bypass and only a few hours later lack intravenous access; one plausible explanation for the question of how this subject happened to be without intravenous access is inadequate sedation leading to the subject pulling out her own lines.

### 7.3.4 Significant Adverse Events

Treatment-emergent adverse events, while in some cases underestimated, were frequent, occurring in 63.6% of subjects. A high incidence of adverse events is somewhat expected, however, given the severity of underlying illness in these intubated, sedated subjects in the pediatric intensive care unit. The Applicant also reported that only 2.5% of TEAEs were severe, 15.7% drug-related, 4.1% leading to study discontinuation, 2.8% serious, and none resulting in an outcome of death. The Applicant defined TEAEs of special interest as bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, hypotension, diastolic hypotension, hypertension, diastolic hypertension, and systolic hypertension, and noted these occurred in 25.1 percent of subjects in the total population, with 8.5 percent, or 27, requiring intervention. Of those 27, eleven had hypotension. Most of these data are presented in the following table, provided by the Applicant (Table 37).

**Table 37 Overview of Adverse Events by PWR-Specified Age Group - Safety Population**

| Subjects with Type of Event | Age Group I Neonatal (N = 42) n (%) | Age Group II 1 mo - < 6 mos (N = 60) n (%) | Age Group III 6 mo - < 12 mo (N = 55 n (%) | Age Group IV 12 mo - <24 mo (N = 51) n (%) | Age Group V 2 yr - < 6 yr (N = 54) n (%) | Age Group VI 6 yr - ≤ 16 yr (N = 57) n (%) | DEX Total (N = 319) n (%) |
|---|---|---|---|---|---|---|---|
| Subjects with one or more TEAEs | 26 (61.9%) | 29 (48.3%) | 41 (74.5%) | 29 (56.9%) | 38 (70.4%) | 40 (70.2%) | 203 (63.6%) |
| Subjects with one or more severe TEAEs | 1 (2.4%) | 0 (0.0%) | 1 (1.8%) | 2 (3.9%) | 2 (3.7%) | 2 (3.5%) | 8 (2.5%) |
| Subjects with one or more drug-related TEAEs[1] | 3 (7.1%) | 9 (15.0%) | 12 (21.8%) | 10 (19.6%) | 7 (13.0%) | 9 (15.8%) | 50 (15.7%) |
| Subjects with AE with outcome of death | 1 (2.4%) | 0 (0.0%) | 3 (5.5%) | 2 (3.9%) | 0 (0.0%) | 0 (0.0%) | 6 (1.9%) |
| Subjects with TEAE with outcome of death | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Subjects with one or more SAEs | 2 (4.8%) | 6 (10.0%) | 9 (16.4%) | 7 (13.7%) | 3 (5.6%) | 2 (3.5%) | 29 (9.1%) |
| Subjects with one or more treatment-emergent SAEs | 1 (2.4%) | 2 (3.3%) | 4 (7.3%) | 1 (2.0%) | 0 (0.0%) | 1 (1.8%) | 9 (2.8%) |
| Subjects with one or more drug-related SAEs[1] | 0 (0.0%) | 1 (1.7%) | 3 (5.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4 (1.3%) |
| Subjects with one or more drug-related treatment-emergent SAEs[1] | 0 (0.0%) | 1 (1.7%) | 3 (5.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4 (1.3%) |
| Subjects who discontinued study drug for one or more TEAEs | 0 (0.0%) | 4 (6.7%) | 4 (7.3%) | 3 (5.9%) | 0 (0.0%) | 2 (3.5%) | 13 (4.1%) |
| Subjects with one or more TEAEs of special Interest[2] | 4 (9.5%) | 18 (30.0%) | 23 (41.8%) | 14 (27.5%) | 9 (16.7%) | 12 (21.1%) | 80 (25.1%) |
| Subjects with one or more TEAEs of special Interest requiring intervention[3] | 4 (9.5%) | 5 (8.3%) | 5 (9.1%) | 2 (3.9%) | 4 (7.4%) | 7 (12.3%) | 27 (8.5%) |

N = Number of subjects in the Safety Population in the given PWR Age Group.
n = number of Safety Population subjects in the given PWR Age Group with the particular type of event.
(1) Drug related includes certain, definitely related, possible, possibly and probably related to study drug.
(2) Includes bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, hypotension, diastolic hypotension, hypertension, diastolic hypertension, and systolic hypertension.
(3) Includes bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, hypotension, diastolic hypotension, hypertension, diastolic hypertension, and systolic hypertension of sufficient severity to require medical intervention.
Abbreviations: AE = adverse event; PWR = pediatric written request; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: End-of-Text Table 4.1.1, End-of-Text Table 4.1.3.2.

The true incidence of adverse events is higher than reported by the Applicant, however. As described in 7.3.3, there was at least one subject, DEX-08-05 Subject 27303, who had a hypotensive incident that seems to qualify as a drug-related TEAE of special interest requiring intervention; the study drug was stopped and no adverse event recorded.

Also worth consideration is the incidence of adverse events that required intervention, the incidence of which was reported to be only 8.5 percent. However, the reviewer is unable to verify which TEAEs required intervention and which did not, due to absence of information about doses and timing of concomitant medications. For example, DEX-08-05 Subject 11203, as described in 7.3.2, had milrinone and epinephrine infusions during DEX, with unknown start times and no documentation of infusion adjustment, a halving of the DEX dose during those vasoactive infusions, and a TEAE of decreased central venous pressure.

However, adverse event frequency according to my review largely does not exceed the labeled incidence in adults; those adverse events that may have occurred more frequently in these subjects than in adults were acidosis, agitation, rage or anger, fever, tachycardia, hypertension, atrioventricular block, hypokalemia, hypophosphatemia, vomiting, hyperglycemia, stridor, and hypoxia. However, the data is confounded by

concomitant medication administration, and in the absence of a placebo group or distinct dose ranges for comparison, the events and their incidences would be misleading if attributed, in labeling, to DEX.

### 7.3.5 Submission Specific Primary Safety Concerns

While there are several relatively frequent adverse events during the trials, the data is confounded such that adverse effects cannot be attributed to DEX. A primary issue is the absence of information surrounding adverse events. Adverse events of the cardiovascular system were the most common, but hemodynamic parameters were not recorded during these adverse events, and the protocols did not provide definitions for hypotension, hypertension, tachycardia, and bradycardia, that would constitute an adverse event. Therefore, the presence or absence of the cardiovascular adverse events of greatest incidence and great importance was determined by investigator discretion, or for some of the trials, by attainment of a dose-limiting toxicity (of which there were none).

Moreover, the only vital signs provided for confirming the presence and severity of adverse events were those performed times at specified in the protocols. In the example of DEX-08-05, vital signs were to be recorded every five minutes during DEX loading, and after 15 mins, 30 mins, 1 hour, 4 hours, and every four hours thereafter, and within 5 minutes of discontinuation, hourly for six hours thereafter, and then every four hours until 24 hours post-DEX. In addition, vital signs were obtained immediately prior to and five minutes after any rescue medication administration. This prescribed vital sign documentation leaves a number of four-hour windows for hemodynamic lability, and investigator discretion for determining what degree of hypotension would warrant an adverse event.

A concerning example of an adverse event without documented blood pressures is a subject that died and whose first adverse event was hypotension; the six month-old had no blood pressure documented during the episode of moderate hypotension. Blood pressures were provided at hour one, before onset of the 100 minute hypotensive episode, and at hour four, after the hypotensive episode, but not during; a blood pressure at hour eight that the investigator did not label as an adverse event, and therefore for was probably of lesser severity, was 71/37. At hour twelve, the subject's blood pressure wasn't much higher. This example points to the question: How low is low enough to qualify as an adverse event? (b) (4) A conclusion about adverse event incidence cannot reasonably be made without additional data points that the Applicant has not provided and does not have.

Hypotension was a common adverse event, and was associated with deaths and non-fatal serious adverse events as described in Sections 7.3.1 Deaths and 7.3.2 Nonfatal Serious Adverse Events. However, its incidence has been underestimated. Hypotension was not defined *a priori*, and therefore, many cases of hypotension were not classified as adverse events, leading to an underestimation of incidence of this important risk of DEX administration.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The following treatment-emergent adverse events occurred in at least two percent of the DEX-exposed subjects. Many were discussed in Section 7.3. Also discussed in 7.3 were the reasons that the data is too confounded to consider these adverse events as accurately representing the adverse event profile of DEX for pediatric ICU sedation.

**Table 38 Adverse Events with 2% or Higher Incidence - Safety Population**

| Preferred Term | Events | Number of subjects | Proportion of Subjects (%) |
|---|---|---|---|
| Hypertension | 220 | 59 | 18% |
| Hyperglycaemia | 67 | 44 | 14% |
| Hypotension | 121 | 42 | 13% |
| Pyrexia | 40 | 39 | 12% |
| Hypokalaemia | 45 | 36 | 11% |
| Tachycardia | 69 | 21 | 7% |
| Vomiting | 24 | 23 | 7% |
| Atelectasis | 16 | 16 | 5% |
| Agitation | 14 | 13 | 4% |
| Anaemia | 13 | 13 | 4% |
| Bradycardia | 14 | 14 | 4% |
| Nausea | 13 | 13 | 4% |
| Pleural effusion | 15 | 13 | 4% |
| Hypocalcaemia | 9 | 8 | 3% |
| Hypothermia | 8 | 8 | 3% |
| Oxygen saturation decreased | 12 | 9 | 3% |
| Pain | 9 | 9 | 3% |
| Pneumothorax | 10 | 10 | 3% |
| Pulmonary oedema | 11 | 11 | 3% |
| Stridor | 10 | 10 | 3% |
| Anger | 8 | 6 | 2% |
| Diarrhoea | 6 | 6 | 2% |
| Drug withdrawal syndrome | 5 | 5 | 2% |
| Infusion site extravasation | 5 | 5 | 2% |
| White blood cell count increased | 5 | 5 | 2% |

### 7.4.2 Laboratory Findings

Laboratory abnormalities were frequent, but may not be attributable to DEX. The Applicant reported that for most laboratory analyses, between five and twenty percent of the values fell outside the normal range. However, the Applicant considered abnormal only those values that were normal during baseline assessment, while providing the percentage abnormal post-infusion among all subjects, which is an inappropriate denominator if an abnormal pre-infusion laboratory excludes a subject from being considered abnormal post-infusion. The difference in percentage of abnormal labs based upon selected denominator is significant, because only 6142 of 9853 baseline laboratories (62.3 percent) were considered normal. The out-of-range values are presented by the Applicant in the following table (Table 39).

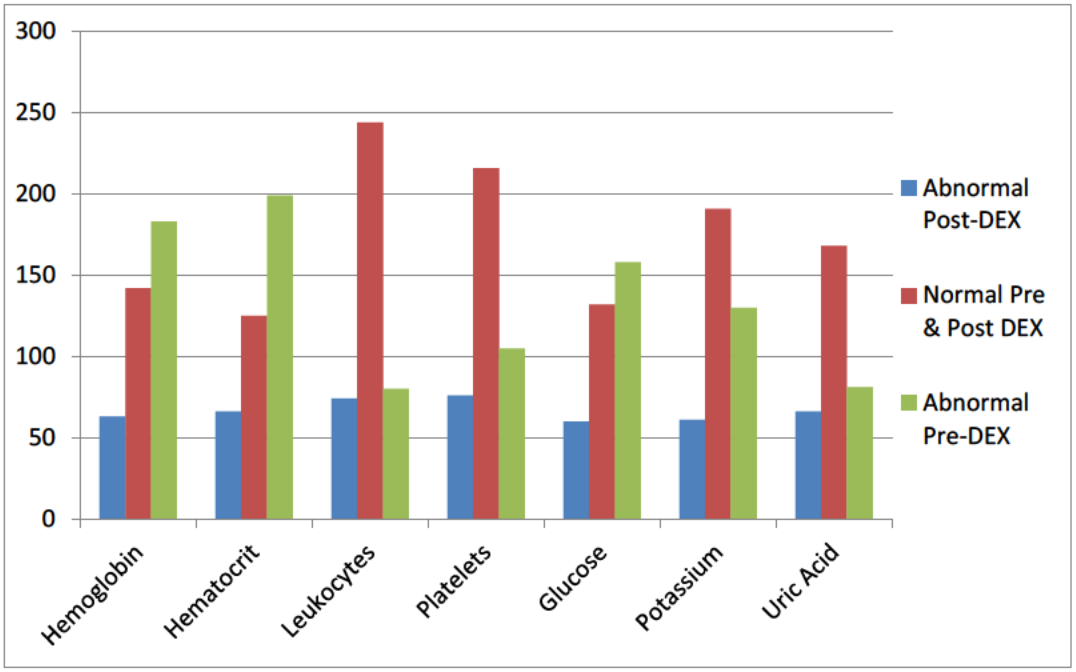
**Table 39 Incidence of Out-of-Range Laboratory Values by PWR-Specified Age Group**

| Laboratory Category Analyte (unit) | PDL-1 Neonatal (N = 42) n (%) | PDL-2 (N = 131) n (%) | PDL-3 (N = 146) n (%) | DEX Total (N = 319) n (%) |
|---|---|---|---|---|
| **Hematology** | | | | |
| Basophils (%) | 1 (2.4%) | 1 (0.8%) | 5 (3.4%) | 7 (2.2%) |
| Eosinophils (%) | 4 (9.5%) | 8 (6.1%) | 13 (8.9%) | 25 (7.8%) |
| Erythrocytes (x $10^{12}$/L) | 4 (9.5%) | 20 (15.3%) | 23 (15.8%) | 47 (14.7%) |
| Hematocrit (%) | 8 (19.0%) | 29 (22.1%) | 29 (19.9%) | 66 (20.7%) |
| Hemoglobin (g/L) | 7 (16.7%) | 25 (19.1%) | 31 (21.2%) | 63 (19.7%) |
| Leukocytes (x $10^9$/L) | 8 (19.0%) | 28 (21.4%) | 38 (26.0%) | 74 (23.2%) |
| Lymphocytes (%) | 8 (19.0%) | 23 (17.6%) | 21 (14.4%) | 52 (16.3%) |
| Monocytes (%) | 7 (16.7%) | 23 (17.6%) | 28 (19.2%) | 58 (18.2%) |
| Neutrophil Band Forms (%) | 4 (9.5%) | 5 (3.8%) | 13 (8.9%) | 22 (6.9%) |
| Neutrophils (%) | 12 (28.6%) | 23 (17.6%) | 24 (16.4%) | 59 (18.5%) |
| Platelets (x $10^9$/L) | 6 (14.3%) | 30 (22.9%) | 40 (27.4%) | 76 (23.8%) |
| **Chemistry** | | | | |
| Alanine Aminotransferase (U/L) | 7 (16.7%) | 12 (9.2%) | 10 (6.8%) | 29 (9.1%) |
| Albumin (g/L) | 3 (7.1%) | 23 (17.6%) | 17 (11.6%) | 43 (13.5%) |
| Alkaline Phosphatase (U/L) | 3 (7.1%) | 6 (4.6%) | 8 (5.5%) | 17 (5.3%) |
| Aspartate Aminotransferase (U/L) | 7 (16.7%) | 21 (16.0%) | 19 (13.0%) | 47 (14.7%) |
| Bilirubin (µmol/L) | 1 (2.4%) | 5 (3.8%) | 10 (6.8%) | 16 (5.0%) |
| Blood Urea Nitrogen (mmol/L) | 4 (9.5%) | 28 (21.4%) | 26 (17.8%) | 58 (18.2%) |
| Calcium (mmol/L) | 2 (4.8%) | 14 (10.7%) | 22 (15.1%) | 38 (11.9%) |
| Creatinine (µmol/L) | 0 (0.0%) | 7 (5.3%) | 15 (10.3%) | 22 (6.9%) |
| Glucose (mmol/L) | 5 (11.9%) | 25 (19.1%) | 30 (20.5%) | 60 (18.8%) |
| Magnesium (mmol/L) | 2 (4.8%) | 17 (13.0%) | 22 (15.1%) | 41 (12.9%) |
| Phosphorus (mmol/L) | 7 (16.7%) | 20 (15.3%) | 27 (18.5%) | 54 (16.9%) |
| Potassium (mmol/L) | 8 (19.0%) | 24 (18.3%) | 29 (19.9%) | 61 (19.1%) |
| Protein (g/L) | 4 (9.5%) | 18 (13.7%) | 27 (18.5%) | 49 (15.4%) |
| Sodium (mmol/L) | 6 (14.3%) | 18 (13.7%) | 32 (21.9%) | 56 (17.6%) |
| Uric Acid (µmol/L) | 7 (16.7%) | 22 (16.8%) | 37 (25.3%) | 66 (20.7%) |
| **Urinalysis** | | | | |
| Blood | 3 (7.1%) | 20 (15.3%) | 18 (12.3%) | 41 (12.9%) |
| Glucose | 2 (4.8%) | 6 (4.6%) | 7 (4.8%) | 15 (4.7%) |
| Ketones | 4 (9.5%) | 11 (8.4%) | 14 (9.6%) | 29 (9.1%) |
| Protein | 4 (9.5%) | 14 (10.7%) | 7 (4.8%) | 25 (7.8%) |
| Specific Gravity | 0 (0.0%) | 7 (5.3%) | 8 (5.5%) | 15 (4.7%) |
| pH | 0 (0.0%) | 7 (5.3%) | 5 (3.4%) | 12 (3.8%) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with the particular out-of-range analyte.
An out-of-range laboratory value is a post-infusion value that is outside the normal range when the baseline value is normal.
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr.
Abbreviations: g = gram; hr = hour; kg = kilogram; L = liter; µmol = micromole; mcg = microgram; mmol = millimole; PDL = pediatric dose level; U = unit.
Source: End-of-Text Table 7.2.1.

The laboratories with the most frequent abnormalities were hemoglobin, hematocrit, leukocytes, platelets, glucose, potassium, and uric acid. Given that half of the subjects had surgery requiring cardiopulmonary bypass and all were pediatric intensive care unit patients receiving many other medications, the laboratory abnormalities are not unexpected nor striking enough to be attributed to DEX. The following graph demonstrates, not surprisingly given the subjects' diseases and post-operative states, a 40-50 percent incidence of abnormal hemoglobin, hematocrit, and glucose among subjects who were normal at baseline, and the high incidence of abnormal baseline values. While clinically important, these laboratory abnormalities may not be attributable to DEX.

**Figure 12 Number of Subjects with Laboratory Abnormalities - Safety Population**




One concerning case involving an absence of information was a subject with "liver failure" that did not have a final set of laboratories as required by the protocol. The subject's LFT elevation is a concern, but it is also noteworthy that the subject's liver function was abnormal at baseline. The subject had a 28-day follow-up and was reportedly okay. Nonetheless, the subject had a four-fold increase in ALT and was not evaluated and followed in accordance with the protocol. Given the limited laboratory data, cannot be concluded that this subject, who was admitted for croup, had a return to baseline liver function. The relevant laboratory results are shown below ().

**Table 40 Laboratory Results for DEX-08-05 Subject 24307**

| | Screening (Hour -2.7) | Post Study Drug Administration (Hour 27) | Within 24 Hours of Discharge or Hospital Day 5-7 | Units |
|---|---|---|---|---|
| Albumin | 3.5 | 3.9 | Not Done | g/dL |
| Alkaline Phosphatase | 207 | 197 | Not Done | U/L |
| Alanine Aminotransferase | 75 | 305 | Not Done | U/L |
| Aspartate Aminotransferase | 257 | 209 | Not Done | U/L |
| Bilirubin | 0.1 | 0.2 | Not Done | mg/dL |
| Platelet | 175 | 157 | Not Done | K/UL |

### 7.4.3 Vital Signs

There may be signals of hemodynamic perturbations, including bradycardia and hypotension, within the vital signs data, although the Applicant's assessment of vital sign abnormalities is problematic for a number of reasons. First, ten percent of protocol-required measurements were not recorded. Second, the values that were considered abnormal for a particular age group vary by study, and the values considered normal by the Applicant deviate from published norms. Third, the values that were considered abnormal were not determined *a priori* and differ from accepted norms (Table 41). Fourth, the Applicant's conclusions about incidence of abnormalities is flawed because vital signs were not recorded frequently enough to adequately characterize potential fluctuations; vital sign recording was most frequent during the first hour of DEX and the first six hours after DEX discontinuation; outside those windows, recording of these ICU patients' vital signs was every four hours and around the time of rescue medication administration.

**Table 41 Range of Normal Heart Rate in Beats per Minute by Age for Selected Trials with Reference Values**

| Study | 1 – ≤2mos | >2 – ≤6mos | >6 – ≤12mos | >12 – ≤24mos | >2 – ≤6yrs | >6 – ≤12yrs | >12 – ≤16yrs |
|---|---|---|---|---|---|---|---|
| DEX-08-01 | n/a | n/a | n/a | n/a | 71-120 | 61-110 | 51-95 |
| DEX-08-05 | 90-150 | 80-150 | 80-150 | 70-120 | 60-110 | 60-110 | 50-95 |
| CHOP | 91-149 | 81-119 | 81-119 | 71-109 | n/a | n/a | n/a |
| *Reference*[6] | *80-160* | | | *80-130* | *75-120* | *65-110* | *60-105* |

Note: wks = weeks; mos = months; yrs = years
*Normal for boys: aged 14: 60-100; aged 16: 65-95. Normal for girls: aged 14: 65-105; aged 16: 60-100.

The Applicant's determination of abnormal heart rate was reportedly based upon their review of the literature, and their normal values vary between studies and deviate from published normal values. Therefore, the approximately four percent incidence of abnormally low heart rate underestimates the true incidence of low heart rate among subjects over the age of twelve months. For example, using the Applicant's definition of normal, a subject aged two years with a heart rate of 71 would be considered normal, when the normal range according to the Nelson Textbook of Pediatrics for a two-year old is 80 to 130 with an average of 110.

Conversely, the nearly 70 percent incidence of abnormally high heart across rate across age groups may be an overestimation because the Applicant's upper limit of normal is lower than the reference normal. Also contributing to the high incidence of abnormally

[6] Kliegman, Robert M., Stanton, Bonita M.D., St. Geme, Joseph, Schor, Nina F., Behrnman, Richard E. *Nelson Textbook of Pediatrics.* Philadelphia: Saunders, 2011.

high heart rate and particularly striking is the 31 beat-per-minute difference between the upper limit of normal for subjects aged >2 months to ≤12 months and enrolled in CHOP versus DEX-08-05.

While consensus normal ranges for blood pressure in pediatric patients are not readily found, the Applicant's definitions of normal systolic blood pressure seem, in this reviewer's opinion and as was the case with heart rate, bent towards not considering unacceptably low blood pressure as low (Table 42). Therefore, the roughly ten percent incidence of abnormally low blood pressure and four percent incidence of abnormally low heart rate cannot be relied upon to reflect the true incidence.

**Table 42 Range of Normal Systolic Blood Pressure in mmHg by Age and Study with Reference Values**

| Study | 28-<36wks | ≥36-≤44wks | 1-≤2mos | >2-≤6mos | >6-≤12mos | >12-≤24mos | >2-≤6yrs | >6-≤12yrs | >12-≤16yrs |
|---|---|---|---|---|---|---|---|---|---|
| DEX-09-08 | 35-75 | 40-75 | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| DEX-11-06 | 35-75 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| DEX-08-01 | n/a | n/a | n/a | n/a | n/a | n/a | 80-120 | 80-120 | 90-135 |
| DEX-08-05 | n/a | n/a | 60-90 | 60-90 | 70-105 | 70-105 | 80-120 | 80-120 | 90-135 |
| CHOP | n/a | n/a | 46-84 | 56-89 | 66-104 | 66-104 | n/a | n/a | n/a |
| DEX-11-01 | n/a | n/a | n/a | n/a | n/a | 70-105 | n/a | n/a | n/a |
| *NHLBI*[7] | *n/a* | *n/a* | *n/a* | *n/a* | *n/a* | *99-102** | *103-110** | *109-120** | *121-130** |
| *Cote*[8] | *50†* | *65-75††* | *95††* | *n/a* | *95††* | *100††* | *n/a* | *105-115††* | *n/a* |
| *AHA*[9] | *n/a* | *60-84* | *73-94* | *78-103* | *82-105* | *85-103* | *88-106* | *96-115* | *110-131* |

Note: wks = weeks; mos = months; yrs = years; NHLBI = National Heart, Lung, and Blood Institute
* 90th percentile for systolic blood pressure among subjects in 50th percentile for height, for column-specified ages
† Mean systolic blood pressure for preterm infants at 0-12 hours of life
†† Mean systolic blood pressure

The Applicant's upper limit for normal is, at least in certain age groups, unacceptably high. The Applicant has classified systolic blood pressures above 120 mmHg for subjects aged >12 to ≤ 16 years as normal, when the upper limit of normal is widely accepted as 120 mmHg. In addition, the Applicant's definition of normal for subjects

[7] National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114 (2 suppl 4th report):555– 576

[8] Cote, Charles J., Todres, I. David, Ryan, John F., and Goudsouzian, Nishan G. *A Practice of Anesthesia for Infants and Children.* Philadelphia: Saunders, 2001.

[9] Pediatric Advanced Life Support Provider Manual. http://www heart.org/idc/groups/heart-public/@wcm/@ecc/documents/downloadable/ucm_436697.pdf. Accessed May 17, 2013.

younger than twelve consistently includes blood pressures above the range considered normal by the National Heart, Lung, and Blood Institute, leading to an underestimation of the number of subjects with abnormally high blood pressure.

The Applicant has identified a high incidence of abnormally high heart rate or blood pressure during and after DEX infusion, and a relatively low incidence of abnormally low heart rate and blood pressure, as presented in the following table (Table 43).

**Table 43 Incidence of Vital Sign Abnormalities by Time of Assessment by Pediatric Dose Level - Safety Population**

| Time of Assessment<br>Vital Sign | PDL-1<br>Neonatal | PDL-2 | PDL-3 | DEX Total |
|---|---|---|---|---|
| Baseline | (N = 42)<br>n (%) | (N = 131)<br>n (%) | (N = 146)<br>n (%) | (N = 319)<br>n (%) |
| Abnormally Low | | | | |
| Heart Rate (beats/min) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Systolic Blood Pressure (mmHg) | 0 (0.0%) | 2 (1.5%) | 7 (4.8%) | 9 (2.8%) |
| Abnormally High | | | | |
| Heart Rate (beats/min) | 7 (16.7%) | 69 (52.7%) | 87 (59.6%) | 163 (51.1%) |
| Systolic Blood Pressure (mmHg) | 12 (28.6%) | 49 (37.4%) | 42 (28.8%) | 103 (32.3%) |
| Study Drug Infusion | (N = 42)<br>n (%) | (N = 131)<br>n (%) | (N = 146)<br>n (%) | (N = 319)<br>n (%) |
| Abnormally Low | | | | |
| Heart Rate (beats/min) | 0 (0.0%) | 5 (3.8%) | 8 (5.5%) | 13 (4.1%) |
| Systolic Blood Pressure (mmHg) | 0 (0.0%) | 16 (12.2%) | 17 (11.6%) | 33 (10.3%) |
| Abnormally High | | | | |
| Heart Rate (beats/min) | 21 (50.0%) | 98 (74.8%) | 102 (69.9%) | 221 (69.3%) |
| Systolic Blood Pressure (mmHg) | 23 (54.8%) | 84 (64.1%) | 101 (69.2%) | 208 (65.2%) |
| Post-Study Infusion | (N = 42)<br>n (%) | (N = 130)<br>n (%) | (N = 145)<br>n (%) | (N = 317)<br>n (%) |
| Abnormally Low | | | | |
| Heart Rate (beats/min) | 0 (0.0%) | 4 (3.1%) | 7 (4.8%) | 11 (3.5%) |
| Systolic Blood Pressure (mmHg) | 0 (0.0%) | 17 (13.1%) | 12 (8.3%) | 29 (9.1%) |
| Abnormally High | | | | |
| Heart Rate (beats/min) | 14 (33.3%) | 102 (78.5%) | 107 (73.8%) | 223 (70.3%) |
| Systolic Blood Pressure (mmHg) | 24 (57.1%) | 99 (76.2%) | 98 (67.6%) | 221 (69.7%) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with the particular vital sign abnormality during the given time period.
Source: 5.3.5.3 ISS Table 121, p. 198

Regarding changes in vital signs, the time points selected for analysis by the Applicant do not reflect the extent of vital sign fluctuation experienced during and after infusion, giving the appearance of less hemodynamic perturbations from the study drug than were observed. Characterization of maximum blood pressure changes, that is, an evaluation of the change from baseline to lowest (or, in some cases, highest) vital sign value would have been far more informative of the degree of vital sign lability during DEX.

Nonetheless, the Applicant's first comparison was between baseline vital signs and final vital signs taken during the infusion, and the Applicant concluded that the mean and median changes from baseline to final value were small across all groups for systolic and diastolic blood pressure, oxygen saturation, and temperature. While factually true, large standard deviation and ranges of change suggest large hemodynamic changes, at least among certain patients. The following table includes these data regarding blood pressure and heart rate changes, as provided by the Applicant (Table 44).

**Table 44 Change from Baseline Value to Final Value of Vital Signs During Infusion by Pediatric Dose Level - Safety Population**

| Vital Sign (unit)<br>Baseline Assessment<br>Change to Final Assessment | PDL-1 Neonatal (N = 42) | PDL-2 (N = 131) | PDL-3 (N = 146) | DEX Total (N = 319) |
|---|---|---|---|---|
| **Systolic Blood Pressure (mmHg)** | | | | |
| Baseline | | | | |
| n | 42 | 131 | 146 | 319 |
| Mean (SD) | 67.7 (15.68) | 101.6 (16.29) | 99.4 (16.99) | 96.2 (19.91) |
| Median (Range) | 66.5 (42.0 - 105.0) | 99.0 (70.0 - 161.0) | 98.0 (64.0 - 150.0) | 96.0 (42.0 - 161.0) |
| Change to Final | | | | |
| n | 42 | 131 | 146 | 319 |
| Mean (SD) | -0.3 (11.74) | -0.4 (19.30) | 0.9 (18.94) | 0.2 (18.27) |
| Median (Range) | 1.0 (-40.0 - 28.0) | -3.0 (-55.0 - 52.0) | 2.0 (-60.0 - 55.0) | 0.0 (-60.0 - 55.0) |
| **Diastolic Blood Pressure (mmHg)** | | | | |
| Baseline | | | | |
| n | 42 | 131 | 146 | 319 |
| Mean (SD) | 40.3 (12.45) | 55.1 (12.75) | 53.4 (11.86) | 52.4 (13.17) |
| Median (Range) | 38.5 (23.0 - 79.0) | 53.0 (21.0 - 118.0) | 52.0 (21.0 - 86.0) | 51.0 (21.0 - 118.0) |
| Change to Final | | | | |
| n | 42 | 131 | 146 | 319 |
| Mean (SD) | -0.1 (12.82) | -0.2 (14.13) | 2.1 (12.78) | 0.9 (13.36) |
| Median (Range) | 0.5 (-44.0 - 38.0) | 0.0 (-46.0 - 45.0) | 1.0 (-34.0 - 36.0) | 0.0 (-46.0 - 45.0) |
| **Heart Rate (beats/minute)** | | | | |
| Baseline | | | | |
| n | 42 | 131 | 146 | 319 |
| Mean (SD) | 150.3 (17.94) | 129.5 (25.70) | 128.6 (29.23) | 131.8 (27.44) |
| Median (Range) | 149.0 (124.0-182.0) | 130.0 (62.0 - 187.0) | 125.0 (66.0 - 205.0) | 132.0 (62.0 - 205.0) |
| Change to Final | | | | |
| n | 42 | 131 | 146 | 319 |
| Mean (SD) | -4.7 (16.64) | -10.6 (21.08) | -15.0 (25.86) | -11.8 (23.11) |
| Median (Range) | -3.0 (-42.0 - 26.0) | -13.0 (-57.0 - 67.0) | -12.5 (-81.0 - 60.0) | -11.0 (-81.0 - 67.0) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with a vital sign value for the time period.
Subjects with missing baseline values or missing during infusion values are not included.
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with LD 0.05 - 0.2 mcg/kg and MD 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with LD 0.25 - 0.5 mcg/kg and MD 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with LD 0.5 - 1.0 mcg/kg and MD 0.5 - 2.0 mcg/kg/hr.
Abbreviation: °C = degrees centigrade; kg = kilogram; LD = loading dose; mcg = microgram; MD = maintenance dose; mmHg = millimeters mercury; PDL = pediatric dose level; SD = standard deviation.
Source: End-of-Text Table 8.1.1.

Source: 5.3.5.3 ISS Table 124, p. 205

Table 43 reveals a possible bradycardia signal, particularly among infants. The table above identifies significant the changes heart rate among all subjects, with an average decrease of 11.8 beats per minute with a standard deviation 23.1, and a remarkable range from an 81 beats per minute decrease in heart rate to a 67 beats per minute

increase. Comparing pediatric age groups, subjects aged 1 to <6 months had the largest average decrease in heart rate (19.5 beats per minute) and also included the subject with largest absolute decrease in heart rate (-81 beats per minute).

The Applicant's second comparison was of was the change in vital signs from final value during infusion to final value following infusion, and they concluded that blood pressure, heart rate, and respiratory rate all increased after discontinuation of DEX. This reviewer agrees with the Applicant's conclusion, but notes again the large standard deviations and ranges, as exhibited below.

**Table 45 Change in Vital Signs from Final Values During Infusion to Final Value Following Infusion by Pediatric Dose Level - Safety Population**

| Vital Sign (unit) End Infuson to- Final Post-Infusion | PDL-1 Neonatal (N = 42) | PDL-2 (N = 131) | PDL-3 (N = 146) | DEX Total (N = 319) |
|---|---|---|---|---|
| **Systolic Blood Pressure (mmHg)** | | | | |
| Final During Infusion | | | | |
| n | 42 | 130 | 145 | 317 |
| Mean (SD) | 67.4 (11.42) | 101.4 (19.78) | 100.5 (17.06) | 96.5 (20.96) |
| Median (Range) | 66.0 (48.0 - 92.0) | 99.0 (66.0 - 153.0) | 98.0 (65.0 - 152.0) | 95.0 (48.0 - 153.0) |
| Change to Final Following Infusion | | | | |
| n | 42 | 130 | 145 | 317 |
| Mean (SD) | 3.2 (9.90) | 1.4 (19.07) | 0.9 (20.14) | 1.4 (18.62) |
| Median (Range) | 4.5 (-16.0 - 25.0) | 3.0 (-53.0 - 45.0) | 3.0 (-73.0 - 48.0) | 3.0 (-73.0 - 48.0) |
| **Diastolic Blood Pressure (mmHg)** | | | | |
| Final During Infusion | | | | |
| n | 42 | 130 | 145 | 317 |
| Mean (SD) | 40.2 (11.32) | 55.1 (14.15) | 55.5 (11.55) | 53.3 (13.62) |
| Median (Range) | 38.5 (22.0 - 87.0) | 54.0 (22.0 - 99.0) | 55.0 (24.0 - 84.0) | 52.0 (22.0 - 99.0) |
| Change to Final Following Infusion | | | | |
| n | 42 | 130 | 145 | 317 |
| Mean (SD) | -0.6 (10.54) | 4.6 (16.01) | 2.7 (14.96) | 3.0 (14.96) |
| Median (Range) | 0.0 (-45.0 - 19.0) | 4.0 (-40.0 - 52.0) | 0.0 (-38.0 - 45.0) | 1.0 (-45.0 - 52.0) |
| **Heart Rate (beats/minute)** | | | | |
| Final During Infusion | | | | |
| n | 42 | 130 | 145 | 317 |
| Mean (SD) | 145.5 (17.46) | 118.8 (24.42) | 113.1 (24.59) | 119.7 (25.84) |
| Median (Range) | 145.5 (110.0 - 183.0) | 121.5 (57.0 - 188.0) | 113.0 (56.0 - 186.0) | 120.0 (56.0 - 188.0) |
| Change to Final Following Infusion | | | | |
| n | 42 | 130 | 145 | 317 |
| Mean (SD) | 3.0 (17.21) | 2.9 (24.21) | 9.8 (24.25) | 6.1 (23.61) |
| Median (Range) | 4.0 (-53.0 - 42.0) | 3.0 (-78.0 - 72.0) | 11.0 (-98.0 - 69.0) | 7.0 (-98.0 - 72.0) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with a vital sign value for the time period.
Subjects with missing final values during infusion or missing final values following infusion are not included.
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with LD 0.05 - 0.2 mcg/kg and MD 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with LD 0.25 - 0.5 mcg/kg and MD 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with LD 0.5 - 1.0 mcg/kg and MD 0.5 - 2.0 mcg/kg/hr.
Abbreviation: °C = degrees centigrade; kg = kilogram; mcg = microgram; mmHg = millimeters mercury; PDL = pediatric dose level; SD = standard deviation.
Source: End-of-Text Table 8.2.1.

Source: 5.3.5.3 ISS Table 125, p. 209

While there is a great deal of concerning vital signs data, no less concerning is the amount of data that is missing. Ten percent of vital signs that were prescribed in the protocol for performance during DEX were not documented. Review of the DEX-08-05 subjects with the lowest blood pressures revealed missing blood pressures at times adjacent to those lows. Two of the patients are described below.

The subject with the single lowest recorded systolic blood pressure in DEX-08-05 was subject 202031, who had no adverse events and incomplete vital sign documentation. The subject, with a baseline blood pressure of 114/55, had a blood pressure of 52/40 five minutes after DEX was discontinued and missed the previous scheduled blood pressure. Therefore, a six hour window without vital sign documentation preceded this episode of extreme hypotension that was not considered an adverse event.

Similarly, the subject with the second lowest recorded systolic blood pressure in DEX-08-05 was subject 20327, who had no adverse event corresponding with a blood pressure of 55/29 and an extended period of time without vital signs. This subject had an adverse event of hypotension with onset prior to DEX initiation, during which the vital signs ranged between 64/30 and 106/60. The hypotension adverse event resolved shortly after DEX initiation and a blood pressure reading of 66/31. However, the subject's documented blood pressure nadir during DEX was 55/29, after which the subject had no vital signs documented for eleven hours despite study drug administration.

### 7.4.4 Electrocardiograms (ECGs)

The Applicant did not analyze ECGs in the ISS, and this reviewer did not find any ECG-related signals, although ECG data was not provided for the CHOP subjects. Confounding the analysis is the frequency of ECG abnormalities in the ICU population, and particularly the post-cardiac surgery population, which made up more than half of the subjects in these studies.

Despite not analyzing ECGs, the Applicant's ISS identified DEX-related treatment-emergent adverse events, some of which were related to ECGs and are presented in the following table (Table 46).

**Table 46 Incidence of ECG and Cardiac DEX-Related Treatment Emergent Adverse Events by Dose Level - Safety Population**

| Preferred Term | PDL-1 Neonatal (N = 42) n (%) | PDL-2 (N = 131) n (%) | PDL-3 (N = 146) n (%) | DEX Total (N = 319) n (%) |
|---|---|---|---|---|
| AV Block Complete | 0 (0%) | 0 (0%) | 1 (0.7%) | 1 (0.3%) |
| Bradycardia | 0 (0%) | 2 (1.5%) | 5 (3.4%) | 7 (2.2%) |
| Myocarditis | 0 (0%) | 1 (0.8%) | 0 (0%) | 1 (0.3%) |
| Nodal Arrhythmias | 0 (0%) | 0 (0%) | 1 (0.7%) | 1 (0.3%) |
| Nodal Rhythm | 0 (0%) | 1 (0.8%) | 0 (0%) | 1 (0.3%) |
| ECG | 0 (0%) | 1 (0.8%) | 0 (0%) | 1 (0.3%) |
| ECG change | 0 (0%) | 0 (0%) | 1 (0.7%) | 1 (0.3%) |
| ECG ST segment elevation | 0 (0%) | 1 (0.8%) | 0 (0%) | 1 (0.3%) |
| ECG T wave inversion | 0 (0%) | 1 (0.8%) | 0 (0%) | 1 (0.3%) |

N = Number of subjects in the Safety Population in the given PDL Group.
n = number of subjects in the Safety Population in the given PDL Group with the particular event
ECG = electrocardiogram; PDL = pediatric dose level
Includes certain, definitely related, possible, possibly and probably related to study drug. A subject reporting same event > 1 time is counted once for the event, in the most related category.
PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr.
Source: Derived from 5.3.5.3 ISS Table 59, p. 110

DEX did not appear to cause QT interval prolongation, although there were a few cases. Only subjects in DEX-08-05, DEX-09-08, and DEX-11-06 had Fridericia-corrected QT intervals. Among those 188 subjects with Fridericia-corrected QTs, five had a QTc interval of greater than 500 during or after DEX, but two of those five had a prolonged QTc at baseline. In addition, the magnitude of increase in QTc interval over baseline was greater than 30 in only two of the five cases.

Subjects in DEX-08-01 had the Bazzet correction, and QT intervals were not reported, but the dataset listed five subjects with prolonged QT and onset during DEX, and an additional five with prlonged QT and onset after DEX. There were another two subjects reported in the cardiology interpretation as having prolonged QT with onset during and one with onset after DEX. ECG data were not provided for subjects enrolled in CHOP.

Moreover, the ECG dataset contains at least a small amount of erroneous data and review reveals a concerning case of missing information and erroneous classification. DEX-08-05 Subject 01319 had a normal screening ECG, followed by a low heart rate on a mid-infusion ECG, and for an extended period of time before and after that mid-infusion ECG, none of the protocol-required vital signs were recorded. A subsequent ECG was classified in the dataset as performed during study drug administration, but according to the time stamp, the ECG was done more than ten hours after DEX was discontinued. The subject's changes from screening to mid-infusion of heart rate from 130 to 81 and RR interval from 460 to 742 are concerning and may be related to DEX. Meanwhile, the subject did not have an adverse event documented, and the lowest heart rate in the vital signs dataset was 89, recorded at hour 4 of DEX, and the next heart rate was documented at hour 19.5, upon DEX discontinuation (Table 47).

**Table 47 Subject DEX-08-05-01319, Heart Rate Assessments from Hour 4 through 19.5 of DEX and ECGs**

| Time After DEX Initiation (Hours) | Visit | Assess-ment | Heart Rate | ECG Interpretation |
|---|---|---|---|---|
| -4.15 | Screening | ECG | 130 | Normal |
| 4 | Study drug administration | Vital Signs | 116 | 4 hours after start of maintenance infusion |
| 8 | Study drug administration | Vital Signs | Not done | 8 hours after start of maintenance infusion |
| 8.4 | Study drug administration | ECG | 81 | n/a |
| 12 | Study drug administration | Vital Signs | Not done | 12 hours after start of maintenance infusion |
| 16 | Study drug administration | Vital Signs | Not done | 16 hours after start of infusion |
| 16.07 | Study drug administration | ECG | 116 | Abnormal |
| 19.5 | Study drug administration | Vital Signs | 98 | Prior to maintenance infusion discontinuation |
| 19.5 | Post-study drug administration | Vital Signs | 98 | Within 5 minutes after study drug discontinuation |
| 30.91 | Study drug administration | ECG | 142 | Normal |

ECG = electrocardiogram

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Despite no demonstrable difference in efficacy between high and low dose groups, there appears to be a higher incidence of adverse events among members of PDL-3, the higher dose group. Bradycardia, hypotension, tachycardia, and acidosis are concerning adverse events that may be more frequent in the higher dose group, PDL-3. While the dose groups were imperfect, due to dose titration and overlap between groups, most subjects were appropriately placed into group PDL-1, -2, or -3. Dose dependency for adverse events is explored below, considering all adverse events with an incidence of > 1 percent, and incidence of adverse events that are attributed to DEX.

The adverse events with an overall incidence of at least one percent and at least fifty percent higher incidence with increasing dose, as would be most likely if the adverse event was a drug effect, were hypotension, acidosis, tachycardia, bradycardia, pleural effusion, anemia, constipation, sedation, decreased urine output, urinary retention, ST segment elevation, and infusion site extravasation. These adverse events, as reported by the Applicant, with an overall incidence of at least one percent and an increased incidence between dose levels 2 and 3 are identified in Table 48 below.

**Table 48 Adverse Events with > 1% Incidence and Increased from PDL-2 to PDL-3 - Screened Population**

| Body System or Organ Class<br>Dictionary-Derived Term | PDL-1<br>N=42 | PDL-2<br>N=131 | PDL-3<br>N=146 | All Subjects<br>N=365 |
|---|---|---|---|---|
| **Vascular Disoders** | | | | |
| Hypotension | 0 (0%) | 14 (11%) | 28 (19%) | 42 (12%) |
| **Metabolism and Nutrition Disorders** | | | | |
| Hyperglycemia | 2 (5%) | 17 (13%) | 25 (17%) | 44 (12%) |
| Acidosis | 0 (0%) | 1 (0.8%) | 3 (2%) | 4 (1%) |
| **Cardiac Disorders** | | | | |
| Tachycardia | 1 (2%) | 6 (5%) | 14 (10%) | 21 (6%) |
| Bradycardia | 2 (5%) | 3 (2%) | 9 (6%) | 14 (4%) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Atelectasis | 2 (5%) | 6 (5%) | 8 (5%) | 16 (4%) |
| Pleural Effusion | 2 (5%) | 4 (3%) | 7 (5%) | 13 (4%) |
| Pneumothorax | 1 (2%) | 4 (3%) | 5 (3%) | 10 (3%) |
| **Psychiatric Disoders** | | | | |
| Agitation | 0 (0%) | 6 (5%) | 7 (5%) | 13 (4%) |
| **Blood and Lymphatic System Disorders** | | | | |
| Anemia | 3 (7%) | 3 (2%) | 7 (5%) | 13 (4%) |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 0 (0%) | 6 (5%) | 7 (5%) | 13 (4%) |
| Constipation | 0 (0%) | 1 (0.8%) | 3 (2%) | 4 (1%) |
| **Nervous System Disorders** | | | | |
| Sedation | 0 (0%) | 0 (0%) | 4 (3%) | 4 (1%) |
| **Renal and Urinary Disorders** | | | | |
| Urinary Retention | 0 (0%) | 0 (0%) | 4 (3%) | 4 (1%) |
| **Investigations** | | | | |
| Urine Output Decreased | 0 (0%) | 0 (0%) | 4 (3%) | 4 (1%) |
| Electrocardiogram ST Segment Elevation | 0 (0%) | 1 (0.8%) | 3 (2%) | 4 (1%) |
| White Blood Cell Count Increased | 0 (0%) | 2 (2%) | 3 (2%) | 5 (1%) |
| **General DOs and Administration Site Conditions** | | | | |
| Infusion Site Extravasation | 1 (2%) | 1 (0.8%) | 3 (2%) | 5 (1%) |

PDL-1: Neonatal subjects (28 weeks gestational age to <1 month) with loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr.
PDL-2: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr.
PDL-3: Subjects ≥ 1 month to ≤ 16 years of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr.

Despite seemingly inconsistent causality determinations, more adverse events were considered at least possibly related to DEX among the high dose subjects than the low dose subjects. For example, among the twelve adverse events of hypotension that occurred during DEX administration that were determined to be at least possibly related to DEX, one occurred in the PDL-1 group, three in the PDL-2 group, and eight in the PDL-3 group. The pattern of study-drug related increased adverse events among the higher dose group is not limited to hypotension; higher rates of adverse events were reported in the high dose group for adverse of special interest, to include bradycardia, tachycardia, and hypertension, which each occurred in more than twice as many subjects in the PDL-3 group as the PDL-2 group.

Because the possible inconsistency of causality determinations have not been discussed elsewhere, they are mentioned in brief here. The consistency and reliability of causality determination by 40 investigators, particularly among the five open-label studies, is questionable. For example, an adverse event of bradycardia with onset during DEX loading was reported in four subjects; one was classified as probably not related to DEX, one as possibly related, and two as definitely related. This reviewer doesn't agree that, in the case of DEX-08-01 Subject 313018, a decline in heart rate from 83 five minutes prior to DEX initiation to 62 five minutes after DEX initiation is "probably not related" to DEX in a subject whose heart rate, once recovered, never again dropped below 83.

### 7.5.2 Time Dependency for Adverse Events

Adverse events appear to be most common at the time of DEX initiation, as demonstrated in Figure 13 below. Considering only adverse events of special interest, that is, bradycardia, tachycardia, hypotension, and hypertension, one finds a similar, albeit more pronounced, adverse event predominance immediately after DEX initiation, as demonstrated in

Table 48Figure 14.

**Figure 13 Number of Adverse Events by Time After DEX Initiation - Safety Population**

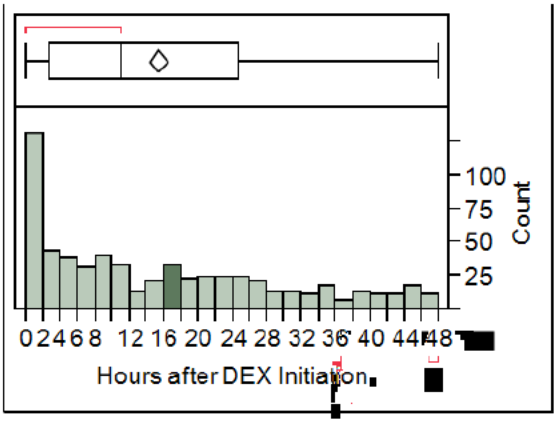
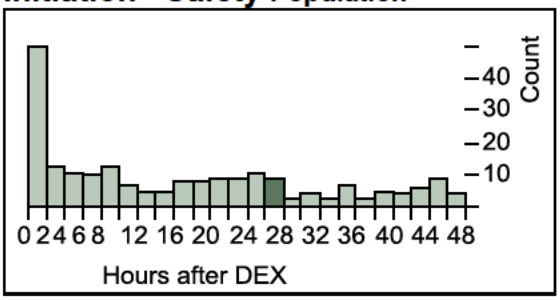



**Figure 14 Number of Adverse Events of Special Interest by Time After DEX Initiation - Safety Population**

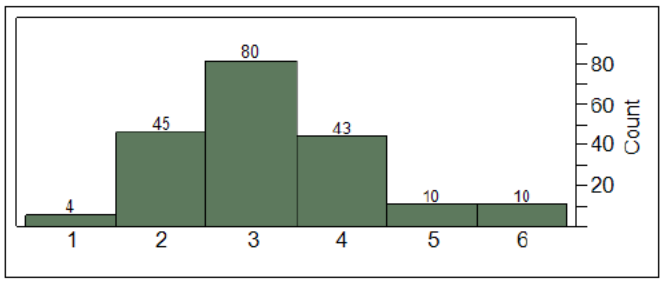



### 7.5.3 Drug-Demographic Interactions

The age group of subjects experiencing the greatest risk for adverse events related to DEX was the non-neonatal infant group, whereas gender and race didn't appear to affect safety. There was a large difference between doses administered to DEX-09-08 and DEX-11-06, who were less than one month of age, and doses administered to subjects enrolled in the other studies, who were one month of age or older, and the lesser susceptibility to adverse events that seemed related to DEX in the youngest group may be related to its relatively low dosing in the youngest group.

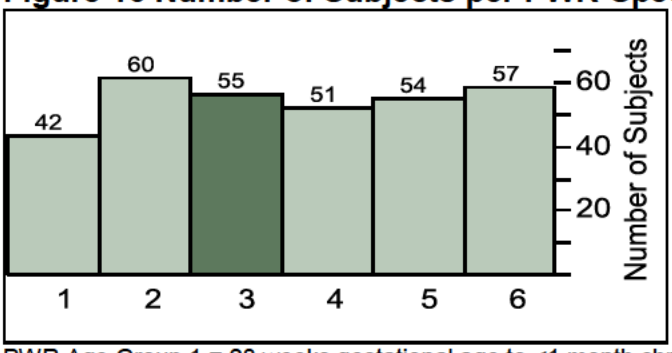
Adverse events of special interest occurring after DEX were most common in the six months to two years age group (PWR Groups 2, 3, and 4), and second most common in the one to six month age group, as demonstrated in Figure 15. For comparison, number of subjects per age group and the relatively even distribution of subjects across PWR-specified age groups are presented in Figure 16.

**Figure 15 Number of Adverse Events by PWR-Specified Age Group - Safety Population**




PWR Age Group 1 = 28 weeks gestational age to <1 month chronological age; PWR Age Group 2 = 1 month to <6 months; PWR Age Group 3 = 6 months to <12 months; PWR Age Group 4 = 12 months to <24 months; PWR Age Group 5 = 2 years to <6 years; PWR Age Group 6 = 6 years to <=16 years

**Figure 16 Number of Subjects per PWR-Specified Age Group**




PWR Age Group 1 = 28 weeks gestational age to <1 month chronological age; PWR Age Group 2 = 1 month to <6 months; PWR Age Group 3 = 6 months to <12 months; PWR Age Group 4 = 12 months to <24 months; PWR Age Group 5 = 2 years to <6 years; PWR Age Group 6 = 6 years to <=16 years

Gender did not appear to impact safety. The safety population consisted of 55.7 percent males, and their adverse event incidence was proportional to their population; 55 percent of all adverse events in the safety population occurring anytime after DEX initiation were in males. Likewise, considering only adverse events of special interest occurring in the 48 hours after DEX initiation, 58 percent were in males.

Some differences in treatment-emergent adverse events by race are possible. There were many more Caucasian than non-Caucasian subjects, although the classification into groups was imperfect. Nonetheless, the Applicant has divided the races into these two groups, and notable in the following table (Table 49) is the higher incidence of gastrointestinal disorders, pyrexia, hypokalemia among Caucasians. Most remarkable is the incidence of hypertension among non-Caucasians, 21 percent versus eleven percent for Caucasians. However, a drug-related difference cannot be concluded based upon these studies that were largely not assessor-blinded and lacked pre-specified definitions of hypertension.

**Table 49 Incidence of Common Treatment-Emergent Adverse Events by PDL and by Race - Safety Population**

| Common TEAE SOC Preferred Term | PDL-1 Neonatal (N = 42) | | PDL-2 (N = 131) | | PDL-3 (N = 146) | | DEX Total (N = 319) | |
|---|---|---|---|---|---|---|---|---|
| | Caucasian (N = 36) n (%) | Non-Caucasian (N = 6) n (%) | Caucasian (N = 99) n (%) | Non-Caucasian (N = 32) n (%) | Caucasian (N = 109) n (%) | Non-Caucasian (N = 37) n (%) | Caucasian (N = 244) n (%) | Non-Caucasian (N = 75) n (%) |
| # of Any Events | 48 | 5 | 192 | 60 | 197 | 57 | 437 | 122 |
| # of Subjs with ≥ 1 Event | 23 (63.9%) | 3 (50.0%) | 66 (66.7%) | 18 (56.3%) | 70 (64.2%) | 23 (62.2%) | 159 (65.2%) | 44 (58.7%) |
| **Common TEAEs** | | | | | | | | |
| Cardiac Disorders | | | | | | | | |
| Bradycardia | 0 (0.0%) | 1 (16.7%) | 2 (2.0%) | 0 (0.0%) | 5 (4.6%) | 1 (2.7%) | 7 (2.9%) | 2 (2.7%) |
| Tachycardia | 1 (2.8%) | 0 (0.0%) | 2 (2.0%) | 1 (3.1%) | 6 (5.5%) | 0 (0.0%) | 9 (3.7%) | 1 (1.3%) |
| Gastrointestinal Disorders | | | | | | | | |
| Nausea | 0 (0.0%) | 0 (0.0%) | 6 (6.1%) | 0 (0.0%) | 5 (4.6%) | 0 (0.0%) | 11 (4.5%) | 0 (0.0%) |
| Vomiting | 1 (2.8%) | 0 (0.0%) | 6 (6.1%) | 1 (3.1%) | 7 (6.4%) | 1 (2.7%) | 14 (5.7%) | 2 (2.7%) |
| General Disorders and Administration Site Conditions | | | | | | | | |
| Pyrexia | 0 (0.0%) | 0 (0.0%) | 14 (14.1%) | 1 (3.1%) | 9 (8.3%) | 2 (5.4%) | 23 (9.4%) | 3 (4.0%) |
| Metabolism and Nutrition Disorders | | | | | | | | |
| Hyperglycemia | 1 (2.8%) | 0 (0.0%) | 10 (10.1%) | 4 (12.5%) | 16 (14.7%) | 6 (16.2%) | 27 (11.1%) | 10 (13.3%) |
| Hypokalemia | 3 (8.3%) | 0 (0.0%) | 16 (16.2%) | 0 (0.0%) | 9 (8.3%) | 0 (0.0%) | 28 (11.5%) | 0 (0.0%) |
| Psychiatric Disorders | | | | | | | | |
| Agitation | 0 (0.0%) | 0 (0.0%) | 3 (3.0%) | 1 (3.1%) | 3 (2.8%) | 2 (5.4%) | 6 (2.5%) | 3 (4.0%) |
| Anger | 6 (16.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 6 (2.5%) | 0 (0.0%) |
| Respiratory, Thoracic and Mediastinal Disorders | | | | | | | | |
| Atelectasis | 2 (5.6%) | 0 (0.0%) | 1 (1.0%) | 2 (6.3%) | 5 (4.6%) | 3 (8.1%) | 8 (3.3%) | 5 (6.7%) |
| Pleural Effusion | 2 (5.6%) | 0 (0.0%) | 0 (0.0%) | 3 (9.4%) | 3 (2.8%) | 2 (5.4%) | 5 (2.0%) | 5 (6.7%) |
| Pneumothorax | 0 (0.0%) | 0 (0.0%) | 1 (1.0%) | 1 (3.1%) | 3 (2.8%) | 2 (5.4%) | 4 (1.6%) | 3 (4.0%) |
| Pulmonary Edema | 1 (2.8%) | 0 (0.0%) | 3 (3.0%) | 1 (3.1%) | 1 (0.9%) | 1 (2.7%) | 5 (2.0%) | 2 (2.7%) |
| Vascular Disorders | | | | | | | | |
| Hypertension | 1 (2.8%) | 0 (0.0%) | 12 (12.1%) | 7 (21.9%) | 14 (12.8%) | 9 (24.3%) | 27 (11.1%) | 16 (21.3%) |
| Hypotension | 0 (0.0%) | 0 (0.0%) | 6 (6.1%) | 4 (12.5%) | 18 (16.5%) | 5 (13.5%) | 24 (9.8%) | 9 (12.0%) |

N = Number of Total, Caucasian or Non-Caucasian Safety Population subjects, respectively, in the given PDL Group.
n = number of Total, Caucasian or Non-Caucasian Safety Population subjects, respectively, in the given PDL Group with the particular event.
Common TEAEs are defined as TEAEs that occur with an incidence of ≥ 2% in the integrated Safety Population (combined Caucasian and Non-Caucasian) plus "anger" as a TEAE of interest in PWR Age Group I. A subject reporting same event ≥ 1 time is counted only once for the event. PDL-1: Neonatal subjects (28 wks gestational age to <1 mo) with loading dose 0.05 - 0.2 mcg/kg and maintenance dose 0.05 - 0.2 mcg/kg/hr; PDL-2: Subjects ≥ 1 mo to ≤ 16 yrs of age with loading dose 0.25 - 0.5 mcg/kg and maintenance dose 0.2 - 0.5 mcg/kg/hr; PDL-3: Subjects ≥ 1 mo to ≤ 16 yrs of age with loading dose 0.5 - 1.0 mcg/kg and maintenance dose 0.5 - 2.0 mcg/kg/hr; Abbreviations: PDL = pediatric dose level; TEAE = treatment-emergent adverse event. Source: End-of-Text Table 4.8.1.

**Source: 5.3.5.3 ISS Table 86, p. 143.**

### 7.5.4 Drug-Disease Interactions

Subjects that underwent cardiopulmonary bypass had far more adverse events than did subjects not undergoing cardiopulmonary bypass. Specifically, 92% of adverse events of special interest occurred in the fifty percent of subjects who had cardiopulmonary bypass. Other special interest populations were not studied.

### 7.5.5 Drug-Drug Interactions

Drug-drug interactions were not specifically studied by the Applicant, although the Applicant described frequency of adverse events in subjects receiving other medications of interest. However, in this reviewer's opinion, such analysis of adverse events incidence in this study of a non-homogeneous population of intensive care unit subjects who each received an average of approximately 35 medications during the study is too confounded to be potentially meaningful.

Regarding medications for treating hemodynamic perturbations, there was a difference in treatment-emergent adverse events between groups. Over 70 percent of subjects who received medications for hemodynamic instability had an incidence of treatment-emergent adverse events, versus a 48 percent incidence among subjects not receiving such medications. Similarly, approximately 80 to 90 percent of subjects receiving antihypertensives had a treatment-emergent adverse event versus 59 percent of subjects that did not receive antihypertensives.

Administration of opiates and benzodiazepines did not affect the incidence of treatment-emergent adverse events. Regarding opiates, the Applicant reported that only four percent of subjects had not received opiates, during study, and that the incidence of treatment-emergent adverse events was not different between subjects receiving and not receiving opiates. Similarly, 79 percent of subjects had received benzodiazepines, and the difference in incidence of treatment-emergent adverse events between groups was small.

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/s/

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LEAH H CRISAFI
05/23/2013

CHRISTOPHER D BREDER
05/23/2013
Signed off with comment to be included in my CDTL memo