2.0 SYNOPSIS

Name of Sponsor: Hospira, Inc.

Name of Finished Product: Precedex™ (dexmedetomidine HCL Injection)

Name of Active Ingredient: Dexmedetomidine HCL (DEX)

Title of Study: 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

Investigators and Study Center(s): This was a multicenter study; 29 investigative sites participated in this study. A list of Investigators is appended (Appendix 16.1.4) to this report.

Publication (reference): Not applicable

Study Period: 14 January 2010 (First subject, First visit) to 12 January 2011 (Last subject, Last visit)

Phase of Development: 3

Objectives:

The objectives of this study 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 pediatric intensive care unit subjects; and
- to explore the exposure-response relationship between dose of DEX and clinical measures of sedation and safety.

Methodology: This was a phase III, randomized, double-blind, multicenter, dose-controlled study evaluating the safety and efficacy of DEX in initially intubated and mechanically ventilated pediatric subjects in the pediatric intensive care setting. The study population consisted of initially intubated and mechanically ventilated pediatric subjects, aged 1 month (if premature, corrected for gestational age until 3 months of actual birth age) of age through <17 years old, that required sedation in an intensive care setting for up to 24 hours. A total of 175 subjects were enrolled. Subjects were randomized into 1 of 2 treatment groups. Within each treatment group, the loading and maintenance doses were stratified according to the presence or absence of cardiopulmonary bypass (CPB).

Treatment Groups:

Diagnosis	Group 1 **Low dose DEX**	Group 2 **High dose DEX**
s/p CPB	Loading dose: 0.2 mcg/kg Maintenance dose titration range (0.025 – 0.5 mcg/kg/hr)	Loading dose 0.5 mcg/kg Maintenance dose titration range (0.1 – 0.7 mcg/kg/hr)
All other diagnoses	Loading dose 0.3 mcg/kg Maintenance dose titration range (0.05 – 0.5 mcg/kg/hr)	Loading dose 0.6 mcg/kg Maintenance dose titration range (0.2 – 1.4 mcg/kg/hr)

The efficacy and safety parameters monitored included sedation levels, heart rate (HR), blood pressure

(BP), withdrawal, tachydysrhythmias, acute respiratory distress syndrome, and ventilation indicators. Clinical laboratory tests were performed per standard of care, and reviewed by the Investigator for potential adverse events (AEs) throughout the study. Adrenal dysfunction was monitored in a subset of study sites where cortisol levels were drawn at baseline and an adrenocorticotropic hormone stimulation test was conducted at the conclusion of DEX infusion. Once subjects met site-specified respiratory criteria, they underwent tracheal extubation. The DEX infusion could be continued during and after extubation if further sedation was required post-extubation. The continuous infusion of DEX was administered for a minimum of 6 hours for the subject to be considered evaluable, and for a maximum of 24 hours. Sedation levels, HR, BP, respiratory rate (RR), ventilator settings, pulse oximetry (SpO_2), and if available, transcutaneous carbon dioxide ($TcCO_2$) and/or arterial blood gases (ABG), were monitored and recorded in the peri-extubation period.

Number of Subjects:

Planned: An estimated 175 subjects were planned to be enrolled.

Enrolled: A total of 175 subjects were enrolled.

Analyzed: Subjects were randomized into 1 of 2 treatment groups; 89 subjects were randomized to Group 1 (low dose DEX) and 86 subjects were randomized to Group 2 (high dose DEX). All randomized subjects qualified for the Safety Evaluable (SE) population, and 83 subjects in the low dose group and 81 subjects in the high dose received randomized DEX for at least 6 hours and were included in the Efficacy Evaluable (EE) Population.

Diagnosis and Main Criteria for Eligibility: Subjects were 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 DEX, and was anticipated to require a minimum of 6 hours of continuous intravenous (IV) sedation. Subjects also had to have an American Association of Anesthesiologists (ASA) classification of 1, 2, 3, or 4, and a University of Michigan Sedation Scale (UMSS) score of 1, 2, 3, or 4 at the start of infusion of DEX. Eligibility criteria are provided in detail in Sections 9.3.1 and 9.3.2 of the clinical study report.

Test Product, Dose and Mode of Administration, Batch Number: PRECEDEX™ Dexmedetomidine hydrochloride injection (Manufacturer: Hospira, Inc.). For subjects s/p CPB, the low dose DEX group was titrated between 0.025-0.5 mcg/kg/hr and the high dose DEX group was titrated between 0.1-0.7 mcg/kg/hr; for all other diagnoses, the low dose DEX group was titrated between 0.05-0.5 mcg/kg/hr and the high dose DEX groups was titrated between 0.2-1.4 mcg/kg/hr. Batch number: 77-372DK

Duration of Treatment: The continuous infusion of DEX was administered for a minimum of 6 hours for the subject to be considered evaluable and for a maximum duration of 24 hours.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

Criteria for Evaluation:

Primary Efficacy Variable:

The primary efficacy variable was the percentage of subjects that did not require rescue midazolam (MDZ) for sedation based on achieving and maintaining a target a UMSS range of 1-3 while intubated.

Secondary Efficacy Variables:

The secondary efficacy variables were as follows:

- Absolute time and percentage of time on study drug that the subject was in a UMSS range of 1-3 while intubated.
- Absolute time and percentage of time on study drug the subject was out of the target sedation range while intubated (UMSS 0 or 4).

- Total amount of rescue medication required for sedation and analgesia while intubated.
- Time to (successful) extubation. Time to extubation was estimated from the first termination of mechanical ventilation within the DEX infusion until 24-hour follow-up. If ventilation settings were not available and the subject discontinued DEX because IV sedation was no longer required, the extubation date/time was estimated as the end of study drug date/time.
- Time to first dose of rescue medication for sedation and analgesia.

Safety Variables:

- AEs
- Vital signs (BP, mean arterial pressure, HR, RR, SpO_2, $TcCO_2$, ABG [if available], core body temperature and body weight)
- Laboratory results
- Input/output fluid balance while on DEX
- 12-lead electrocardiogram (ECG)
- Use of rescue medications to support the vital signs
- Prior, concomitant and adjunct medications
- Incidence of withdrawal (after discontinuation of DEX infusion)

Statistical Methods: The statistical analyses were performed using SAS®, version 9.1. All statistical tests were 2 sided and p values ≤ 0.0500, after rounding to 4 decimal places, were considered statistically significant unless otherwise specified. For continuous variables, N, mean, median, SD, minimum, Q1, Q3 and maximum are presented. For categorical variables, N and percent is shown. The primary efficacy dataset was the EE Population. Efficacy analyses based on the SE Population dataset were performed as a secondary. Unless otherwise noted, the same analyses were performed for the EE or SE datasets. All efficacy variables were analyzed while on DEX. Subjects were also grouped by age (age group I: subjects ≥1 month to <24 months old; age group II: subjects ≥24 month to <17 years old).

Analysis of Primary Efficacy Variable:

The percentage of subjects that did not require rescue MDZ for sedation based on achieving and maintaining a target a UMSS range of 1-3 while intubated was summarized for each treatment group with descriptive statistics (N, SD, median, min, Q1, Q3, and max). The difference between treatment groups was assessed as risk differences for 2x2 tables with 95% confidence interval with and without a continuity correction using PROC FREQ in SAS. Additionally, differences between treatment groups adjusting for underlying condition or age group were assessed using Mantel-Haenszel (MH) test in PROC FREQ.

Analysis of Secondary Efficacy Variables:

- Absolute time and percentage of time on study drug that the subject is in a UMSS range of 1-3 while intubated: If 1 of the consecutive UMSS measurements was out of 1-3 range, a linear interpolation was used between them to estimate the time within the UMSS range 1-3 and above or below this range. If there were several UMSS scores at 1 time, then the average of these scores was used. The absolute time that the subject was in a UMSS range of 1-3 while intubated was calculated for each subject as the total amount of time where the estimated UMSS scores are in the UMSS range of 1-3. The percentage of interest was derived then as a ratio of the time in UMSS range of 1-3 to the total time while intubated during the study.
- Absolute time and percentage of time on study drug the subject was out of the target sedation range while intubated (UMSS 0 or 4) were summarized for each treatment group with descriptive statistics (N, mean, SD, median, min, Q1, Q3, and max). The difference between treatment groups in the absolute times and percents was assessed using Wilcoxon test with PROC NPAR1WAY.
- The total amount of rescue medication MDZ, morphine or fentanyl given for sedation and analgesia was summarized for each treatment group with descriptive statistics (N, mean, SD, median, min, Q1, Q3, and max). The difference between treatment groups was assessed with

PROC NPAR1WAY.

- The time to successful extubation and time to first dose of rescue medication for sedation and analgesia were summarized with Kaplan-Meier estimates. Between treatment groups comparisons were made with log-rank and Wilcoxon tests.

Safety Analysis:

All subjects who received any amount of DEX were included in the SE Population and in the safety analysis. Only the treatment-emergent AEs (TEAEs) were analyzed. However, all AEs are presented in the data listings. The number and percentage of subjects with TEAEs were summarized for each age group overall and by dose level according to Medical Dictionary for Regulatory Activities system organ class and preferred term. Category of AE severity and category of AE relationship to DEX were similarly summarized. Similar summaries were made for serious AEs. Treatment differences in incidence of each AE were assessed by Fisher's exact test.

The absolute value and change from baseline in vital signs was summarized descriptively for each of the mean, minimum, and maximum value by dose level/underlying condition/age. The number and percentage of subjects with clinically significant abnormal laboratory values at the baseline, during DEX infusion, and during the follow-up period was summarized by dose level/underlying condition/age. Other safety variables were summarized descriptively.

SUMMARY – CONCLUSIONS

DEMOGRAPHICS:

- Median age of age groups combined was 10.7 months (range: 0.9 months to 16.3 years) in the low dose group and 14.7 months (range: 1.3 months to 16.2 years) in the high dose group. Height and weight were similar across dose groups and by underlying condition (median height of age groups combined: low dose 68.0 cm, high dose 76.5 cm; median weight of age groups combined: low dose 8.1 kg; high dose 8.5 kg). Slightly more subjects overall were male than female (low dose, 59.6% male; high dose, 55.8% male). Demographics were similar between treatment groups with most subjects critically ill from severe congenital cardiopulmonary disease (ASA P3).

EFFICACY RESULTS:

- DEX was clinically effective at sedating critically ill, initially intubated infants and children following major cardiac surgery with CPB and non-cardiac surgery. There was a non-significant ($p = 0.2751$) dose-response effect observed with more subjects (54.3%) in the high dose DEX groups not requiring rescue MDZ to maintain the target sedation than in the low dose DEX groups (44.6%), irrespective of age. High dose DEX was most effective in the heart surgery subjects (s/p CPB) with more subjects of both age groups who received high dose DEX than low dose DEX not requiring MDZ sedation rescue ($p = 0.0974$, difference = 22.73%).
- All age groups and diagnoses receiving the high dose of DEX were in the target UMSS range (1-3) 87.8 to 99.2% of the time compared to 85.5 to 99.0% of the time in the low dose DEX groups; the difference was not statistically significant.
- Whereas the median amount (total and per kg) of rescue MDZ for sedation and rescue fentanyl and morphine was not statistically significantly different between the low and high dose DEX groups, total and per/kg doses of rescue MDZ for sedation, rescue fentanyl for analgesia, and rescue morphine for analgesia trended higher in the low dose DEX group.
- Median time from start of DEX infusion to first dose of rescue medication for sedation or fentanyl or morphine for analgesia was 1.6 hours (95% CI: 0.93, 3.38) in the low dose group and was 2.0 hours (95% CI: 1.07, 3.75) in the high dose group; the difference was not statistically significant.
- There were no statistically significant differences between treatment groups for time to extubation.

SAFETY RESULTS:

- DEX was safe and well tolerated in all age groups. DEX was well-tolerated at all doses studied in both cardiac and non cardiac critically ill subjects. No clinical difference between the safety profile of the low and high dose was found. The AE profile is typical of this critically ill high risk pediatric population following major cardiac and non-cardiac surgery. The most commonly reported TEAEs, hypotension and bradycardia, are expected effects from alpha-2 agonists.
- The average maintenance dose of DEX in mcg/kg/hr in the low dose was 0.33 mcg/hr/hr with s/p CPB subjects requiring slightly less maintenance infusion to maintain target sedation. Similarly, in the high dose DEX group the maintenance infusion averaged 0.59 mcg/kg/hr, with s/p CPB subjects requiring less maintenance infusion. No subjects experienced dose-limiting toxicity.
- There was no evidence of a clinically significant mean change in any laboratory parameter or in vital signs, physical examination, or ECG. There was no adrenal suppression and subjects studied had a normal response to adrenocorticotropic hormone in both low and high dose DEX groups.

CONCLUSION:

DEX was effective at sedating initially intubated critically ill infants and children following major cardiac surgery with CPB and non-cardiac surgery. DEX was well-tolerated at all doses studied in both cardiac and non-cardiac critically ill subjects.

Date of the report: 22 July 2011