2.0 SYNOPSIS

Name of Sponsor: Hospira, Inc.

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

Name of Active Ingredient: Dexmedetomidine Hydrochloride (HCl)

Title of Study: A Phase II/III, Open-Label, Multicenter, Safety, Efficacy and Pharmacokinetic Study of Dexmedetomidine in Neonates Ages ≥ 28 Weeks to ≤ 44 Weeks Gestational Age

Investigators and Study Center(s): This multicenter study was conducted at 18 investigative sites (9 investigative sites that enrolled 30 subjects for the interim analyses) in this report; a list of Investigators is found in the appendices.

Publication (reference): Not applicable

Study Period: 27 July 2010 to 09 April 2011 for these interim analyses

Phase of Development: Phase II/III

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

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

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

Number of Subjects:

Planned: An estimated 42 subjects, admitted to the intensive care unit (ICU) were to be enrolled in the study. The interim analyses in this report used the completion of study data for the subjects who signed the informed consent and entered the trial prior to 15 April 2011.

Enrolled and Analyzed: A total of 30 subjects were enrolled prior to 15 April 2011, received DEX, and completed the treatment: 6 subjects in age group I (dose level 1) and 24 subjects in age group II (dose levels 1 to 3). These 30 subjects comprised the Enrolled Population (EP). The Intent-to-Treat (ITT), Efficacy Evaluable (EE), and Safety Evaluable (SE) Populations were identical to the EP and comprised the same 30 subjects who received DEX for ≥ 6 hours. The Pharmacokinetic (PK) Evaluable Population was the primary analysis population for the PK analyses and was comprised of 16 subjects who received a minimum of 6 hours of DEX infusion with adequate DEX concentration data to calculate pharmacokinetic parameters. There were 3 subjects in age group I (dose level 1) and 13 subjects in age group II (dose levels 1 to 3).

Diagnosis and Main Criteria for Eligibility: Initially intubated and mechanically ventilated preterm neonates ≥ 28 weeks through < 36 weeks gestational age and term neonates born at ≥ 36 weeks through ≤ 44 weeks gestational age in an intensive care setting anticipated to require a minimum of 6 hours of continuous IV sedation. Weight at the time of enrollment had to be > 1000 g.

Test Product, Dose and Mode of Administration, Batch Number or Test Device: The loading dose of DEX could be diluted in 0.9% sodium chloride or dextrose 5% in water to one of the following concentrations:

- 4 mcg/mL solution, or
- 2 mcg/mL solution, or
- 1 mcg/mL solution, or
- 0.5 mcg/mL solution.

Batch Numbers: 95-261-DK and 77-372-DK

Duration of Treatment: Each subject received a loading dose of DEX over 10 or 20 minutes followed by the appropriate continuous infusion maintenance dose of DEX for a minimum of 6 but not more than 24 hours.

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

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint for the study was the incidence of subjects requiring any rescue medication (midazolam [MDZ]) for sedation during DEX infusion.

Secondary efficacy endpoints included:

- Incidence of rescue medication use for analgesia during DEX infusion
- (a) The total amount and (b) the weight adjusted total amount (per kg) of rescue medication of MDZ, morphine, or fentanyl given for sedation and analgesia during DEX infusion
- Change from baseline in vital signs (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP], respiration rate [RR], and oxygenation [SpO_2]) during DEX infusion
- Time spent with a total Neonatal Pain, Agitation and Sedation Scale (N-PASS) score $>$ 3 and $\leq$ 3 during DEX infusion
- Time to extubation was explored in DEX-exposed subjects

The primary PK parameters were as follows:

- CL (plasma clearance) and
- CL_w (weight adjusted CL).

Safety: Safety variables included:

- Incidence of AEs
- Change from baseline in vital signs (HR, SBP, DBP, MAP, RR, SpO_2), temperature, and body weight
- Change from screening in clinical laboratory tests
- Change in input/output fluid balance
- Change from baseline in electrocardiograms (ECGs)
- Use of rescue regimens to support vital signs
- Use of adjunct medications
- Incidence of signs of withdrawal (changes in blood pressure [BP] or HR) after discontinuing DEX infusion

Statistical Methods: The statistical analyses were performed using SAS, version 9.1. For these interim analyses, descriptive statistics were used.

SUMMARY

EFFICACY RESULTS:

- Dexmedetomidine was effective at sedating critically ill, initially intubated and mechanically ventilated premature infants, ≥ 28 to < 36 weeks. No subject in age group I received rescue MDZ for sedation during DEX infusion. At the doses used in this trial, up to 0.2 mcg/kg/hr, DEX was effective at sedating term neonates. In age group II, a total of 4 subjects (16.7%) received rescue MDZ (mean dose 0.22 mg/kg) for sedation during DEX infusion.
- Most premature neonates in age group I did not require additional medication for pain while on DEX infusion. One subject (16.7%) in age group I received rescue medication for analgesia during the study infusion. In contrast, more of the term neonates in age group II (58.3%) received rescue medication for analgesia during the study infusion. The increased analgesic requirements in age group II, in particular dose level 3, most likely reflects the higher proportion of post-operative surgical subjects.
- Subjects in all dose levels spent a low period of time with a total N-PASS score > 3 indicating most subjects were adequately sedated and not manifesting signs of pain/agitation.
- Generally, trends in mean change from baseline in vital signs were not clinically meaningful.

PHARMACOKINETIC RESULTS:

- Premature neonates, ≥ 28 to < 36 weeks gestational age, appeared to have lower clearance than term neonates which resulted in higher dose-adjusted exposure. The lower clearance in this age group and higher concentrations are consistent with the greater efficacy observed in the premature neonates (no subjects required rescue MDZ for sedation and 1 subject required rescue medication for analgesia) compared to the term neonates (4 subjects required rescue MDZ for sedation and 14 subjects required rescue medication for analgesia).
- Dexmedetomidine exposure appeared to be dose proportional within the term neonates (age group II). Dose proportionality within the premature neonates (age group I) could not be assessed.
- The volume of distribution at steady state, weight adjusted (V_{ssw}) and the apparent terminal elimination half-life ($t_{1/2)}$ were similar across dose levels and age groups.

SAFETY RESULTS:

- Subjects in age group I received a median total loading dose of 0.07 mcg with a median duration of 10 minutes and a median total maintenance dose of 1.30 mcg over 1407.5 minutes (23.5 hours). Subjects in age group II received a median total loading dose of 0.18 – 0.70 mcg over 10 minutes and a median total maintenance dose of 1.08 – 12.20 mcg over 360 - 961.5 minutes (6 - 16 hours).
- Dexmedetomidine was safe and well tolerated in both age groups and at all doses. The AE profile observed is typical of the critically ill, high risk pediatric population and post-operative surgical patients. TEAEs were experienced by 2 subjects (33.3%) in age group I and by 15 subjects (62.5%) in age group II. In age group I, dose level 1, no TEAEs were reported by more than 1 subject. In age group II, events reported by more than 1 subject were hypokalemia, decreased blood potassium, anger, atelectasis, and pleural effusion. These events were more common and expected in the post-operative open heart surgery subjects.
- Most TEAEs were assessed as not related to treatment, only 2 subjects in the study (in age group II) experienced TEAEs assessed as related to treatment. There were no severe TEAEs reported, 2 subjects in each age group experienced moderate TEAEs, all other subjects experienced mild TEAEs. There were no treatment-emergent SAEs leading to death, no other treatment-emergent SAEs, and no TEAEs that led to DEX discontinuation. There were no dose-limiting toxicities that led to DEX discontinuation (persistent bradycardia, persistent hypotension, or respiratory depression).
- In general, changes from baseline were not clinically significant for laboratory parameters, vital signs, physical examination, or ECGs.

CONCLUSIONS: Dexmedetomidine was effective at sedating critically ill, initially intubated and mechanically ventilated premature infants. No subject in age group I received rescue MDZ for sedation during the study infusion. At the doses used in this trial, up to 0.2 mcg/kg/hr, DEX was effective at sedating term neonates. Most premature neonates in age group I did not require additional medication for pain while on DEX infusion. In contrast, more of the term neonates in age group II (58.3%) received rescue medication for analgesia during the study infusion. The increased analgesic requirements in age group II, in particular dose level 3, most likely reflects the higher proportion of post-operative surgical subjects. Premature neonates appeared to have lower CL than term neonates which resulted in higher dose-adjusted exposure and greater efficacy. No subjects discontinued the trial due to TEAEs. Dexmedetomidine was safe and well tolerated in both age groups and at all doses. The AE profile observed is typical of the critically ill, high risk pediatric population studied.

Date of the report: 15 August 2011