U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 021038
Supplement #:	S-028
Drug Name:	Precedex
Indication(s):	Sedation of non-intubated pediatric patients aged 1 month to 16 years prior to and during non-invasive procedures
Applicant:	Hospira, Inc.
Date(s):	Submitted: 6/17/2022 Wrap-Up Meeting: 11/19/2022 PDUFA: 12/17/2022
Review Priority:	Standard (6 month; pediatric supplement)
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Sue Jane Wang, Ph.D., Supervisory of DAAP Statistical Team, DB1 Deputy Division Director Hsien Ming (Jim) Hung,, Ph.D., DB1 Division Director
Medical Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Clinical Team:	Lisa Banta, M.D., Clinical Reviewer Renee Petit-Scott, Clinical Team Leader (DAAP)
Project Manager:	Rachel Jang (DAAP)

Precedex is currently approved for adult intensive care unit (ICU) sedation and adult procedural sedation. In this submission the applicant is seeking a pediatric indication, specifically "Sedation of non-intubated pediatric patients aged 1 month to 16 years prior to and during non-invasive procedures." An indication for use of Precedex in pediatric patients was sought by the Applicant previously (sub#?) but received a complete Response Letter (CRL) on August 19, 2016. In response to the advice in the letter, the Applicant developed "A Phase 3/4 Randomized, Double-blind, Dose-ranging Study of the Safety and Efficacy of Dexmedetomidine (DEX) Used with Propofol (PRO) As Needed for Procedural Sedation of Pediatric Subjects ~1 Month To <17 Years Of Age Undergoing MRI Scans" (C0801039), which was discussed with DAAP at a Type B meeting in Oct. 2017.

Results from study C0801039 were submitted to support the pediatric indication. The study included 122 subjects in two age cohorts (n=59 in the ≥1 month to <2 years of age group; n=63 in the ≥2 to <17 years age group). There were three treatment arms, defined by the fixed dose level (low; medium; high) which was administered in a blinded manner to achieve procedural sedation during an MRI (magnetic resonance imaging) scan.

The primary endpoint was the percentage of subjects at the Precedex (DEX) high dose level versus the low dose level in the combined age cohorts who did not require concomitant propofol (PRO; rescue sedation) to complete the MRI. The key secondary endpoint was the same comparison but within each of the age cohorts. Additional efficacy endpoints included the percent of time at the target sedation level and other characteristics of procedural sedation and use of concomitant PRO to successfully complete the MRI scan.

The applicant's analyses demonstrated that the high dose level of Precedex had a significantly lower percentage of subjects who required concomitant propofol rescue sedation to complete the MRI scan than the low dose level of Precedex. This was consistent across the two age cohorts. See Applicant's Tables 4 and 6 reproduced below. The results of the other efficacy endpoints were consistent favoring the high dose level of Precedex. I was able to reproduce the Applicant's results for all outcomes of interest for the clinical team.

The study was conducted and analyzed as planned. The results are consistent and provide sufficient evidence in support of the high dose level for procedural sedation in pediatric subjects.

Table 4. Percent of Participants who do not Require Concomitant PRO to Complete MRI (High Dose vs Low Dose)- Mantel-Haenszel Test - Full Analysis Set -(Protocol C0801039)

		High Dose n (%) 95% CI*	Low Dose n (%)95% CI*	Odds ratio 95% CI**	p-value**
Total	N=122	24/38(63.2%)(0.46,0.78)	6/42(14.3%)(0.05,0.29)	0.10(0.03,0.29)	<0.001

Participants that did not require Propofol for sedation based upon achieving target sedation.
Odds ratio was assessed for the difference between treatment groups in percentage of Participants that did not require Propofol for sedation
* Exact 95% CI of proportion of not requiring PRO in each dose level.
**p-values are from PROC FREQ CMH statistics.CI is confidence interval of odds ratio.
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(Database snapshot date : 17DEC2021) Output File: ./cdisc csr/C0801039/adcm s011
Table 14.2.1.1 Dexmedetomidine is for Pfizer internal use.

Source: Clinical Overview, Table 4 Applicant's submission, NDA 021038

Table 6. Percent of Participants who do not Require Concomitant PRO to Complete MRI (High Dose vs Low Dose) by Age Cohort - Mantel-Haenszel Test - Full Analysis Set -(Protocol C0801039)

		High Dose n (%) 95% CI*	Low Dose n (%)95% CI*	Odds ratio 95% CI**	p-value**
>=1mn-<2yr	N=59	9/18 (50.0%) (0.26,0.74)	3/20 (15.0%) (0.03,0.38)	0.18(0.04,0.82)	0.022
>=2yr-<17yr	N=63	15/20 (75.0%) (0.51,0.91)	3/22 (13.6%) (0.03,0.35)	0.05(0.01,0.26)	<0.001

Participants that did not require Propofol for sedation within age group based upon achieving target sedation.
Odds ratio was assessed the difference between treatment groups in Percent of Participants that did not require Propofol for sedation.
* Exact 95% CI of proportion of not requiring PRO in each dose level.
**p-values are from PROC FREQ CMH statistics.CI is confidence interval of odds ratio.
PFIZER CONFIDENTIAL SDTM Creation: 21DEC2021 (06:08) Source Data: adpr Table Generation: 07FEB2022 (07:29)
(Database snapshot date : 17DEC2021) Output File: ./cdisc csr/C0801039/adcm s0221
Table 14.2.1.2 Dexmedetomidine is for Pfizer internal use.

Source: Clinical Overview, Table 6 Applicant's submission, NDA 021038

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/s/

KATHERINE B MEAKER
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changed date

SUE JANE WANG
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