CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Inc

Investigational Product: PF-00914730

Clinical Study Report Synopsis: Protocol C0801039

Protocol Title: 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

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): A total of 21 study sites in the United States and Japan randomized participants in this study. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 18 February 2020 (First Participant First Visit)

Study Completion Date: 30 November 2021 (Last Participant Last Visit)

Report Date: 1 March 2022

Previous Report Date(s): Not applicable

Phase of Development: Phase 3/4

Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Objective	Endpoint
Primary Efficacy Objective:	**Primary Efficacy Endpoint:**
Assess efficacy of DEX for pediatric procedural sedation as measured by the percent of subjects at the high dose level versus the low dose level in the combined age cohorts who did not require concomitant PRO to achieve adequate sedation.	Percent of subjects at the DEX high dose level versus the low dose level in the combined age cohorts who did not require concomitant PRO to complete the magnetic resonance imaging (MRI).
Key Secondary Efficacy Objective:	**Key Secondary Efficacy Endpoint:**
Assess the efficacy of DEX for pediatric procedural sedation as measured by the percent of subjects at the high dose level versus the low dose level in each age cohort who did not require concomitant PRO to achieve adequate sedation.	Percent of subjects at the DEX high dose level versus the low dose level in each age cohort who did not require concomitant PRO to complete the MRI.

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Table S1. Study Objectives and Endpoints

Objective	Endpoint
Secondary Efficacy Objective(s):	**Secondary Efficacy Endpoint(s):**
• Explore the efficacy of DEX at the middle dose level compared to the high dose level and the low dose level in both the overall sample and in each age cohort as measured by the percent of subjects who did not require concomitant PRO to achieve adequate sedation. • Explore the efficacy of DEX by examining the percent of time at the target sedation score, time to first PRO use, emergence time from sedation, proportion of subjects at each dose level receiving PRO and amount of PRO required.	• Percent of subjects at the DEX middle dose level compared to the high dose level and the low dose level in both the overall sample and in each age cohort who did not require concomitant PRO to complete the MRI. • Percent of time at the target sedation rating scale score (Pediatric Sedation State Scale [PSSS] rating of 2) after the administration of the DEX loading dose and during the DEX maintenance infusion. • The amount of time from the start of the DEX loading dose infusion to the time of the first PRO bolus administration. • Emergence time (defined as the time from the end of the MRI scan to when the subject meets a Modified Aldrete Score ≥9). • The proportion of subjects at each DEX dose level who received PRO. • Total amount (mg/kg) and weight and time-adjusted amount (per kg per minute basis) of concomitant PRO required to successfully complete the MRI scan.
Exploratory Objective:	**Exploratory Endpoint:**
Examine the ease of maintenance of overall intra-procedural sedation using DEX.	Anesthesiologist Assessment (a scoring of ease of maintenance of appropriate intra-procedural sedation level, respiratory stability, hemodynamic stability, and subject cooperation).
Safety Objective:	**Safety Endpoints:**
Assess the safety of DEX used for procedural sedation of pediatric subjects undergoing an MRI scan.	• Incidence, seriousness, causality and severity of treatment-emergent adverse events (TEAEs). • Percent of subjects who completed the MRI scan and required artificial ventilation or intervention to restore baseline or normal hemodynamic status. • Mean change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and respiratory rate (RR). • Time outside of the stable range for hemodynamic parameters of SBP and HR. • Incidence of protocol-specified respiratory adverse events (AEs) of bradypnea, hypoxia and apnea. • Incidence of protocol-specified cardiac AEs of hypotension, hypertension and bradycardia. • Incidence of protocol-specified AE of paradoxical agitation reaction. • Incidence of protocol-specified AEs of bradypnea, hypoxia, apnea, hypotension, hypertension, bradycardia and paradoxical agitation reaction requiring intervention. • Incidence of DEX withdrawal-related AEs after discontinuation of DEX infusion.

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METHODS

Study Design: This was a randomized, double-blind, dose-ranging study of the efficacy and safety of DEX when used with PRO as needed, for procedural sedation of pediatric participants ≥1 month to <17 years of age undergoing MRI scans.

This study included Screening, Day 1, Day 2 Follow-up, and Day 29 Long-term Follow-up Visits. The Day 1 Visit comprised a Period 1 (MRI scan) Phase and Period 2 (Post-MRI Recovery) Phase. The Day 2 Visit was a 24-hour follow-up, and the Day 29 Visit was a 28-day follow-up.

A sufficient number of participants were planned to be screened to randomize approximately 120 participants (40 participants per dose level):

Age Cohort	Low Dose Group	Middle Dose Group	High Dose Group
≥1 month to <2 years	20	20	20
≥2 years to <17 years	20	20	20

All eligible participants received double-blind treatment where one of 3 dose levels of DEX were administered. Following completion of required procedures before randomization at the Day 1 Visit, participants meeting entry criteria were randomly assigned to a low, middle or high dose level group (actual dose dependent on age) in a 1:1:1 ratio. Treatment was initiated just prior to the start of the MRI scan and continued through completion of the MRI scan. Concomitant PRO may have been given to ensure adequate sedation.

Diagnosis and Main Criteria for Inclusion: The study population consisted of participants aged ≥1 month and <17 years on Day 1, with American Society of Anesthesiologists Physical Status I, II, or III, who required non-intubated, spontaneous breathing, moderate to deep sedation (NI-MDS) for an MRI study not expected to last >3 hours with an intensivist, anesthesiologist, or other proceduralist in attendance. Participants whose weight at Screening was less than the 10th percentile of weight for age and sex or was greater than the 95th percentile of weight for age and sex (97th percentile in Japan), participants who had a planned medical procedure during the MRI scan or post-MRI recovery period, and participants who required endotracheal intubation or laryngeal mask airway were excluded.

Study Treatment: Participants enrolled into the study were randomized to receive one of 3 DEX dosing regimens (Low, Middle, or High), each consisting of an intravenous (IV) loading dose that was immediately followed by an IV maintenance infusion that continued for the duration of the MRI scan.

The loading and maintenance infusion doses were given at the stable, pre-defined doses as described in Table S2 and Table S3 and were not modified, but the infusion may have been discontinued if clinically indicated. The loading dose was administered over 10 minutes.

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Table S2. Blinded Dose Levels for Participants ≥1 month to <2 years of age on Day 1

Dose Level	DEX Loading Dose	DEX Maintenance Infusion Dose
Low dose level	0.5 mcg/kg	0.5 mcg/kg/hour
Middle dose level	1 mcg/kg	1 mcg/kg/hour
High dose level	1.5 mcg/kg	1.5 mcg/kg/hour

Table S3. Blinded Dose Levels for Participants ≥2 years to <17 years of age on Day 1

Dose Level	DEX Loading Dose	DEX Maintenance Infusion Dose
Low dose level	0.5 mcg/kg	0.5 mcg/kg/hour
Middle dose level	1.2 mcg/kg	1 mcg/kg/hour
High dose level	2 mcg/kg	1.5 mcg/kg/hour

Once the DEX loading dose was administered and the maintenance dose started, if an adequate level of sedation was not achieved within 5 minutes after the start of the DEX maintenance infusion, concomitant PRO may have been given per clinical judgment to ensure that an adequate sedation level was achieved to start the scan. The target sedation level was indicated by a PSSS score of 2 (ie, "Quiet [asleep or awake], not moving during procedure, and no frown [or brow furrow] indicating pain or anxiety. No verbalization of any complaint.").

Concomitant PRO was to be administered as needed through completion of the scan to maintain adequate participant sedation per investigator clinical judgment. If it was needed, PRO was to be administered first as a bolus of 0.5 mg/kg (500 mcg/kg) over approximately 1 minute followed by the start of a PRO maintenance infusion at 50 mcg/kg/min. Additional bolus doses of PRO 0.5 mg/kg may have been given as needed for participant movement/wakening. Following each additional PRO bolus, there must have been a simultaneous increase in the PRO maintenance infusion rate in a 25 or 50 mcg/kg/min increment. However, subsequent increases in the PRO maintenance infusion rate may have been made in 25 or 50 mcg/kg/min increments without a corresponding PRO bolus. The PRO maintenance infusion may have also been decreased in 25 or 50 mcg/kg/min increments as needed to maintain adequate participant sedation, or it may have been discontinued if clinically indicated.

PRO is not approved for procedural sedation in the pediatric population, so in this study the use of PRO was considered investigational.

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Table S4. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Dexmedetomidine hydrochloride injection 200 mcg/2 mL (100 mcg/mL) vial	17-202-DK	20-003225	100 mcg/mL	Solution
	88-105-DK	18-003179		
	06-098-DK	19-003920		
	88-105-DK	18-003376		

Efficacy Evaluations:

Investigational product administration details including start time, stop time and IV rate in mL/hour were recorded on the case report form (CRF).

Concomitant medications and nonpharmacologic therapies were collected from randomization through the Day 29 Long-term Follow-up Visit and were recorded on the CRF and source documents. PRO administration details including start time, stop time, bolus doses in mg/kg and maintenance dose rates in mcg/kg/min were recorded on the CRF.

The PSSS sedation ratings were recorded as part of the anesthesia log on Day 1, Period 1 within approximately 5 minutes prior to the start of the study treatment loading dose infusion, immediately following completion of the loading dose infusion, and at 5 (±1) minute intervals throughout the duration of the study treatment infusion and MRI scan. The PSSS is a validated 6-point scale that is a measurement of the effectiveness and quality of procedural sedation in children. It is specifically designed for evaluating pediatric patients undergoing sedation for diagnostic and therapeutic procedures, and measures aspects of procedural sedation relating to the quality of sedation provided, including the control of pain, anxiety, movement, and adverse side effects.

The Modified Aldrete Score was performed on arrival at the post-procedure recovery area (Day 1, Period 2) and every 15 (±5) minutes until the subject met criteria to leave that area. The Modified Aldrete Score is a validated observational medical scoring system that allows verbal prompts for the measurement of recovery after anesthesia (post anesthesia) which includes activity, respiration, circulation, consciousness and oxygenation. The scores of each item are summed to obtain a total score.

The Anesthesiologist Assessment was completed once the subject was in the post-procedure recovery area (Day 1, Period 2). It is a 4-item rating where each item is scored along a range of “not difficult at all”, “very stable” or “very cooperative” to “extremely difficult”, “extremely unstable” or “extremely uncooperative”. It includes the ease of maintenance of sedation level, hemodynamic stability, respiratory stability and subject cooperation during the MRI scan.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations:
No pharmacokinetic, pharmacodynamic, pharmacogenomic, or other evaluations were done in this study.

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Safety Evaluations: Safety evaluations included serious AEs (SAEs), protocol-specified AEs (changes in BP and HR, paradoxical agitation reactions, and changes in respiratory rate, end-tidal carbon dioxide [$EtCO_2$], and saturation of peripheral oxygen [SpO_2]), prior and concomitant treatments, Pediatric Anesthesia Emergence Delirium Scale (PAED), physical examination, cardiac telemetry, vital signs, and pregnancy test.

The PAED was used to measure emergence delirium in participants post-MRI. It is a 5-item rating scale where each item is scored along a range of "not at all" to "extremely". The scores of each item are summed to obtain a total PAED score where the degree of emergence delirium increases directly with the total score.

Statistical Methods:

The statistical analyses were performed using SAS, version 9.2 or later. All statistical tests were two-sided and p-values ≤0.0500, after rounding to 4 decimal places, were considered statistically significant unless otherwise specified.

Efficacy

Primary Endpoint: The DEX high versus low dose group was compared by Mantel-Haenszel test in PROC FREQ. The difference between high and low dose groups was assessed using odds ratios and 95% confidence intervals (CIs) on the odds ratio. Additionally, 95% CIs on the percent of subjects not requiring supplemental PRO were provided by dose level using exact 95% CIs. All age cohorts were combined. The primary analysis was performed based on the Full Analysis Set (FAS). The same analysis was repeated on the Efficacy Evaluable Population (EEP), the Per Protocol Population (PPP), and the Japanese Population Set (JPS).

Key Secondary Endpoint: The method of analysis for the primary endpoint was repeated for the key secondary endpoint for each age cohort based on the FAS. The same analysis was repeated on the EEP, PPP, and JPS.

Secondary Endpoints: All secondary endpoints were summarized overall and by age cohort for the FAS and JPS.

- **Percentage of subjects at the middle dose level who did not require propofol to complete the MRI**: The method of analysis for the primary endpoint was repeated for the secondary endpoints comparing the low dose to the medium dose and the medium dose to the high dose.

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- **Percentage of time at the target sedation scale**: The difference between dose levels in percent of time at the target sedation rating scale score (PSSS rating of 2) during the DEX maintenance infusion was assessed using the Wilcoxon test. In addition, the difference between dose levels in the percentage of time at PSSS rating of 2 or 3 during the DEX maintenance infusion was assessed using the Wilcoxon test. The percentage of time at the target PSSS rating of 2 during the DEX maintenance infusion with/without PRO was summarized by dose level and age cohort.
- **Time to first propofol bolus administration**: The time to first dose of concomitant PRO was summarized with Kaplan-Meier estimates. Between dose group comparisons were made with log-rank tests. Kaplan-Meier plots of time from the start of DEX loading dose infusion to the time of first PRO bolus infusion were performed by dose level and age cohort.
- **Emergence time**: Time (minutes) from completion of MRI to time a participant first receives an Aldrete score of 9 or greater was summarized using the Kaplan-Meier method. Between dose group comparisons were made with log-rank test. Kaplan-Meier plots of emergence time by dose level and age cohort were performed.
- **Total amount of concomitant propofol**: The total amount (mcg/kg) and the average infusion rate (mcg/kg/min), number of boluses and duration of PRO given for sedation were summarized for each dose level with descriptive statistics. The difference between dose groups (high dose and low dose, and medium dose and low dose and high dose versus medium dose) was assessed using analysis of variance (ANOVA) when assumption of normal distribution is reasonable or by nonparametric tests when this assumption is not met.

Exploratory Endpoint: The Anesthesiologist Assessment was summarized descriptively for each of the 4 items overall and by age cohort.

Safety

Analysis of safety endpoints included TEAEs, DEX withdrawal symptoms, laboratory data, vital signs, MRI scan, and PAED.

All safety analyses were performed on the safety analysis set and JPS.

Descriptive statistics were calculated for quantitative safety data as well as for the change from baseline, when appropriate. Data analyses were presented by dose level, overall and within each age cohort.

TEAEs were analyzed by dose level, overall and by age cohort. However, all AEs were presented in data listings.

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RESULTS

Subject Disposition and Demography:

Of 141 participants screened, 12 participants did not continue to randomization, 1 participant was randomized but not enrolled, and the remaining 128 were randomized and enrolled: 44 to the low dose group, 43 to the middle dose group, and 41 to the high dose group. Six participants were randomized and enrolled but not treated: 2 in the low dose group, 1 in the middle dose group, and 3 in the high dose group. Five participants discontinued study treatment: 3 due to AEs and 2 due to other reasons. All 122 treated participants completed the Day 29 Follow-up Phase.

In the ≥1 month to <2 years age cohort, 59 participants were randomized and treated with DEX: 20 to the low dose group, 21 to the middle dose group, and 18 to the high dose group. Four participants were randomized but not treated: 1 in the low dose group, 1 in the middle dose group, and 2 in the high dose group. Two of 59 participants (3.4%) discontinued study treatment: 1 participant in the low dose group due to an AE and 1 participant in the high dose group due to other (protocol deviation). All 59 treated participants completed Day 1 (Period 1 [MRI scan]) through the Day 29 (Follow-up) Phase.

In the ≥2 years to <17 years age cohort, 63 participants were randomized and treated with DEX: 22 to the low dose group, 21 to the middle dose group, and 20 to the high dose group. Two participants were randomized but not treated: 1 in the low dose group and 1 in the high dose group. Three of 63 participants (4.8%) discontinued study treatment: 2 participants due to AEs (1 each in the middle and high dose groups) and 1 participant in the high dose group due to other (medication error). All 63 treated participants completed Day 1 (Period 1 [MRI scan]) through the Day 29 (Follow-up) Phase.

Note: All 63 treated participants in the ≥2 years to <17 years age cohort completed Day 1 (Period 1); however, 62 participants are reported as completed in the study database. One participant was incorrectly reported as having discontinued Day 1, Period 1.

No participant discontinued from the study due to a COVID-19-related AE.

In the ≥1 month to <2 years age cohort, mean age was similar across dose groups. There was a higher proportion of female participants (60.0%) in the low dose group compared with the middle and high dose groups (42.9% and 44.4%, respectively). Additionally, the proportion of White participants was lower in the middle dose group than in the high and low dose groups, and the proportion of Asian participants was higher in the middle dose group than in the high and low dose groups. Overall, mean age was 0.95 years, and the majority of participants were White or Asian (29 participants [49.2%] and 15 participants [25.4%], respectively).

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In the ≥2 years to <17 years age cohort, demographic characteristics (age, gender, and race) were generally balanced across treatment groups. Overall, mean age was 6.90 years, and the majority of participants were White or Asian (28 participants [44.4%] and 26 participants [41.3%], respectively).

Baseline characteristics (height/body length, weight, temperature) were generally balanced across dose groups in both age cohorts.

Efficacy Results:

Primary Endpoint

A significantly higher percentage of participants at the DEX high dose level completed the MRI without concomitant PRO compared with the DEX low dose level (p<0.001; Table S5).

In the combined age cohorts, an increase in the percentage of participants who did not require concomitant PRO to complete the MRI was observed with increasing DEX dose: 14.3% in the low dose group, 35.7% in the middle dose group, and 63.2% in the high dose group.

Table S5. Percent of Participants who do not Require Concomitant PRO to Complete MRI (High Dose vs Low Dose)- Mantel-Haenszel Test - Full Analysis Set

		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.
PFIZER CONFIDENTIAL SDTM Creation: 21DEC2021 (06:07) Source Data: adpr Table Generation: 07FEB2022 (07:26)
(Database snapshot date : 17DEC2021) Output File: ./cdisc_csr/C0801039/adcm_s011
Table 14.2.1.1 Dexmedetomidine is for Pfizer internal use.

Key Secondary Endpoint

In both age cohorts, a significantly higher percentage of participants at the DEX high dose level completed the MRI without concomitant PRO compared with the DEX low dose level (p≤0.022; Table S6).

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In the ≥2 years to <17 years age cohort, an increase in the percentage of participants who did not require concomitant PRO to complete the MRI was observed with increasing DEX dose: 13.6% in the low dose group, 61.9% in the middle dose group, and 75.0% in the high dose group. In the ≥1 month to <2 years age cohort, there was a higher percentage of participants not requiring PRO in the high dose group (50.0%) compared with the middle and low dose groups (9.5% and 15.0%, respectively).

Table S6. 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

		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.

Secondary Endpoints

- **Percentage of Participants at the DEX Middle Dose Level Not Requiring Propofol:**

  In the combined age cohorts, a significantly higher percentage of participants completed the MRI without concomitant PRO at the DEX middle dose level compared with the DEX low dose level (p=0.024), and at the DEX high dose level compared with the DEX middle dose level (p=0.015).

  In the ≥2 years to <17 years age cohort, a significantly higher percentage of participants at the DEX middle dose level completed the MRI without concomitant PRO compared with the DEX low dose level (p=0.001). A higher percentage of participants at the DEX high dose level completed the MRI without concomitant PRO compared with the DEX middle dose level (p=0.374).

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In the ≥1 month to <2 years age cohort, a significantly higher percentage of participants at the DEX high dose level completed the MRI without concomitant PRO compared with the DEX middle dose level (p=0.006). A similar percentage of participants at the DEX middle and low dose levels completed the MRI without concomitant PRO (p=0.597).

- **Pediatric Sedation State Scale:** In the DEX high dose group, participants in both the combined and individual age cohorts were at the target sedation rating scale score (PSSS of 2) for a mean >87% of the time during the DEX maintenance infusion. In both the combined and individual age cohorts, an increase in the percentage of time at the target sedation rating scale score (PSSS of 2) was observed with increasing DEX dose. The percentage of time at the target sedation rating scale score was significantly higher for participants randomized to the DEX high dose level compared with the DEX low dose level in both the combined and individual age cohorts, supportive of the primary and key secondary endpoint results.

- **Amount of Time to First Propofol Bolus:** In the combined age cohorts, an increase in the time to the first PRO bolus infusion was observed with increasing DEX dose. In both the combined and individual age cohorts, the time to the first PRO bolus infusion was significantly longer for participants randomized to the DEX high dose level compared with the DEX low dose level (p≤0.005), supportive of the primary and key secondary endpoint results.

- **Emergence Time:** No meaningful differences in emergence time (time from completion of MRI to Modified Aldrete score ≥9) were observed between dose levels for the combined age cohorts or either individual age cohort (p≥0.051). In the combined age cohorts, the median emergence time increased with increasing DEX dose: 35.0 minutes (95% CI: 21.0, 41.0) for the low dose, 42.5 minutes (95% CI: 35.0, 52.0) for the middle dose, and 45.5 minutes (95% CI: 35.0, 54.0) for the high dose. A similar pattern was observed for the individual age cohorts.

- **Proportion of Participants who Received Propofol:** In the combined age cohorts and the ≥2 years to <17 years age cohort, a decrease in the proportion of participants receiving PRO was observed with increasing DEX dose.

- **Amount of Propofol Required to Complete the MRI:** Analysis of the amount of PRO required to complete the MRI did not show any notable or significant differences between dose levels for the combined age cohorts or either individual age cohort. In the combined age cohorts, the mean total cumulative PRO dose per kg was lower for the DEX high dose level (3426.4 mcg/kg) compared with the DEX middle or low dose levels (4810.7 and 4828.6 mcg/kg, respectively). Similar results were observed for each age cohort.

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Exploratory Endpoint

Anesthesiologist Assessment: In general, mean anesthesiologist assessment scores (ease of maintenance of sedation level, hemodynamic stability, respiratory stability, and subject cooperation) were low, ranging from 0.7 to 4.6 on a scale from 0 to 10, where 0 equals not difficult at all, very stable, or very cooperative. In each dose group, mean scores were higher for the ≥1 month to <2 years age cohort compared with the ≥2 years to <17 years age cohort.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, Immunogenicity and/or Other Results: No pharmacokinetic, pharmacodynamic, pharmacogenomic, or other evaluations were done in this study.

Safety Results: The proportion of participants with all-causality TEAEs was similar across dose groups (Table S7).

- All TEAEs were mild or moderate; none were severe.
- One participant experienced a treatment-emergent SAE of hypertension. The event was considered moderate in severity and study treatment was withdrawn. In addition, 1 participant experienced severe SAEs of acute respiratory failure and sepsis on Day 30 following planned [redacted] surgery on Day 24, and 1 participant (who underwent an MRI for assessment of an underlying [redacted]) experienced 2 mild SAEs of seizure on Days 2 and 21 that were reported as non-serious by the investigator but upgraded to serious by the sponsor.
- Three participants, 1 in each dose group, discontinued study treatment due to TEAEs (bradycardia, bradypnea, and hypertension)
- No participant discontinued the study due to an AE.
- No deaths were reported during this study.
- No participant reported any AE related to COVID-19.

The proportion of participants with treatment-related TEAEs was higher for the DEX middle dose group (37 participants [88.1%]) than the high and low dose groups (29 participants [76.3%] and 32 participants [76.2%], respectively).

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Table S7. Treatment-Emergent Adverse Events (All Causalities) - Safety Population

Number (%) of Participants	Low Dose n (%)	Middle Dose n (%)	High Dose n (%)	Total n (%)
Participants evaluable for adverse events	42	42	38	122
Number of adverse events	102	96	91	289
Participants with adverse events	38 (90.5)	39 (92.9)	36 (94.7)	113 (92.6)
Participants with serious adverse events	0	0	1 (2.6)	1 (0.8)
Participants with severe adverse events	0	0	0	0
Participants discontinued from study due to adverse events[a]	0	0	0	0
Participants discontinued study drug due to AE and continue Study[b]	1 (2.4)	1 (2.4)	1 (2.6)	3 (2.5)

Includes all data collected since the first dose of study drug.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
b. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Participant to be discontinued from Study
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 21DEC2021 (06:07) Source Data: adae Table Generation: 08FEB2022 (14:39)
(Database snapshot date : 17DEC2021) Output File: ./cdisc_csr/C0801039/adae_s010
Table 14.3.1.2.1 Dexmedetomidine is for Pfizer internal use.

- **Incidence of TEAEs:** The most commonly reported all-causality TEAEs by PT (≥5% participants in any dose group) were bradypnea, bradycardia, hypertension, hypotension, hypoxia, diastolic hypertension, systolic hypertension, tachycardia. In the combined age cohorts and each age cohort, decreases in bradypnea, hypoxia, and hypotension and increases in bradycardia and hypertension were observed with increasing DEX dose.

  The majority of all-causality TEAEs were mild, except for 4 participants who reported moderate all-causality TEAEs: 2 participants in the DEX low dose group (1 participant each with hypoxia and hypotension) and 2 participants in the DEX high dose group (1 participant with bradycardia, and 1 participant with bradycardia, tachycardia, and hypertension). No participant reported a severe all-causality TEAE.

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- **Protocol-Specified Respiratory TEAEs:** Overall, in the combined age cohorts, the most frequently reported protocol-specified respiratory TEAE was bradypnea (82 participants [67.2%]). A decrease in the proportion of participants with bradypnea was observed with increasing DEX dose: DEX low dose level (33 participants [78.6%]), DEX middle dose level (27 participants [64.3%]), and DEX high dose level (22 participants [57.9%]). A similar decrease in hypoxia was observed with increasing DEX dose: DEX low dose level (6 participants [14.3%]), DEX middle dose level (3 participants [7.1%]), and DEX high dose level (1 participant [2.6%]).

- **Protocol-Specified Cardiac TEAEs:** Overall, in the combined age cohorts, the most frequently reported protocol-specified cardiac TEAE was bradycardia (75 participants [61.5%]). A higher proportion of participants at the DEX high dose level (27 participants [71.1%]) reported bradycardia compared with the low and middle dose levels (24 participants [57.1%] each). Increases in bradycardia and, hypertension, and decreases in hypotension were observed with increasing DEX dose, consistent with the known pharmacology of DEX.

- **Protocol-Specified TEAEs Requiring Intervention:** Overall, in the combined age cohorts, 5 participants (4.1%) experienced protocol-specified TEAEs requiring intervention: 2 participants (4.8%) in the low dose group, 1 participant (2.4%) in the middle dose group, and 2 participants (5.3%) in the high dose group. Events of bradycardia requiring intervention were reported by 2 participants, both in the high dose group. All other protocol-specified TEAEs requiring intervention (bradypnea, hypoxia, hypertension, and hypotension) were reported by 1 participant each. Two additional participants experienced TEAEs that required intervention: 1 participant experienced a TEAE of diastolic hypertension that required intervention, but the event was not considered a protocol-specific TEAE, and 1 participant experienced protocol-specified TEAEs of bradypnea and hypoxia that required intervention, but the interventions for these events were reported incorrectly in the CRF; therefore, these events were not included as TEAEs requiring intervention. No participant required artificial ventilation.

- **Withdrawal-Related Adverse Events:** Overall, 3 participants experienced withdrawal-related AEs (1 event of agitation and 2 events of anesthetic complication neurological [investigator entry: emergence delirium]) after discontinuation of the DEX infusion. All the events were considered mild, related to study treatment, and resolved.

- **Vital Signs:** Baseline mean vital sign parameters (HR, blood pressure, respiratory rate, and oxygen saturation) were generally similar within each age cohort for each of the dose levels. Decreases in mean HR, SBP, DBP, and MAP were observed within each age cohort and across dose levels, consistent with the known pharmacology of DEX. At the participant level, decreases that met the protocol-specified threshold for reporting as TEAEs were mild to moderate in severity. Of participants with protocol-specified TEAEs, few required intervention to restore hemodynamic stability and no participant required artificial ventilation.

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- **Hemodynamic Stability:** Overall (total DEX), in both the combined and individual age cohorts, the ratio for the time outside of the hemodynamically stable range was 0.5 or lower, indicating that on average, the time outside of the hemodynamically stable range was less than or equal to half of the time period of evaluation. There were no apparent dose-related effects in the combined age cohorts or in either age cohort.

- **Artificial Ventilation or Intervention:** No participant required artificial ventilation to restore baseline or normal hemodynamic status. Overall, 7 of 122 participants (5.7%) required intervention to restore baseline or normal hemodynamic status. Interventions included atropine, lactated ringer fluids, oxygen supplementation, hydralazine, and glycopyrronium bromide.

- **Pediatric Anesthesia Emergence Delirium Scale:** The mean total PAED score was generally similar across dose groups and age cohorts at the timepoints assessed, with the exception of the ≥1 month to <2 years age cohort at the high dose level. At the time participants first awoke in the recovery area (0 minutes), a total of 11 of 122 participants had a PAED score ≥10: 5 in the high dose group, 2 in the middle dose group, and 4 in the low dose group. With the exception of 2 participants in the ≥1 month to <2 years age cohort at the high dose level, no participant had a PAED score ≥10 within 45 minutes of waking in the recovery area.

Conclusion(s):

Efficacy

The primary objective of the study was met. The DEX high dose level demonstrated clinically meaningful efficacy and was superior to the low dose level to obtain sufficient sedative effect by a single agent for procedural sedation of pediatric participants undergoing MRI scan.

- The DEX high dose level was superior to the low dose level for the primary efficacy endpoint, percent of participants in the combined age cohorts who did not require concomitant PRO to complete the MRI.

- The results for the key secondary efficacy endpoint, percent of participants in each age cohort who did not require concomitant PRO to complete the MRI, were consistent with the overall study population.

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The secondary objectives were met and supported the primary and key secondary endpoint results.

- An increase in the percentage of participants who did not require concomitant PRO to complete the MRI was observed with increasing DEX dose in the combined age cohorts and the ≥2 years to <17 years age cohort. In the ≥1 month to <2 years age cohort, there was a higher percentage of participants not requiring PRO in the high dose group compared with the middle and low dose groups.

- The secondary endpoints of percentage of time at the target sedation rating scale score and the amount of time to first PRO bolus support the results of the primary and key secondary efficacy endpoints.

- In general, mean anesthesiologist assessment scores (ease of maintenance of sedation level, hemodynamic stability, respiratory stability, and subject cooperation) were low.

Safety

The doses of DEX administered in this study for procedural sedation were well tolerated in pediatric participants undergoing an MRI scan and the safety profile is consistent with the known safety profile in adults. All reported TEAEs were mild to moderate in severity and no unexpected TEAEs were reported. Few participants required intervention and no participant required artificial ventilation.